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(56) Documents cited
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GB 1500043
EP 0005129A1
EP 0074341A1
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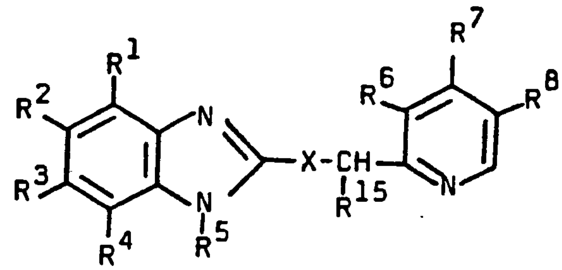
(54) **Novel pharmacologically active compounds**

(57) Novel compounds of the formula:



wherein X is S or SO and $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^{15} are organic residues, pharmaceutical compositions containing such compounds particularly for use in the treatment of gastric disorders.

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2805/5(PHA 4166.5)
Moorman et al.
Express Mail No.: EL801508119US

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SPECIFICATION

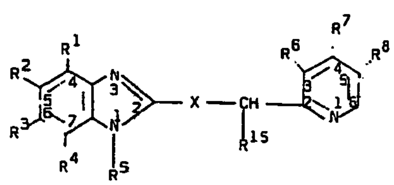
Novel pharmacologically activ c mpounds

The object of the present invention is to provide novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and provide gastrointestinal cytoprotective effects and thus can be used in the prevention and treatment of peptic ulcer.

The present invention relates to the use of the compounds of the invention or therapeutically acceptable salts thereof, for inhibiting gastric acid secretion as well as providing gastrointestinal cytoprotective effects in mammals and man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals and man, including e.g. gastritis, gastric ulcer, and duodenal ulcer. Furthermore, the compounds may be used for prevention and treatment of other gastrointestinal disorders, where cytoprotective and/or gastric antisecretory effect is desirable e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive ethanol consumption. The invention also relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compounds and to novel intermediates in the preparation of the compounds of the invention.

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the British patent specifications 1 500 043 and 1 525 958, in the US patent 4 182 766, in the European patent specification 0 005 129, and in the Belgian patent specification 890 024. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory disease are disclosed in the European patent application with publication no. 0 045 200.

It has been found that the compounds of the formula



I

wherein

X is $-S-$ or $-\overset{O}{\overset{\uparrow}{S}}-$;

R^{15} is H, CH_3 or C_2H_5;

R^1, R^2, R^3 and R^4, which are the same or differ nt, are

(a) H

(b) hal gen

(c) —CN

(d) —CHO

(e) $-CF_3$

(f) $-\overset{O}{\overset{\|}{C}}-R^{11}$

(g) $-O-\overset{O}{\overset{\|}{C}}-R^{12}$

(h) $-CH(OR^{13})_2$

(i) $-(Z)_n-A-D$

(j) aryl

(k) aryloxy

(l) alkylthio containing 1-6 carbon atoms

(m) $-NO_2$

(n) alkylsulfinyl containing 1-6 carbon atoms

or wherein

(o) adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from N and O, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups $(-\overset{O}{\overset{\|}{C}}-)$, whereby if R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same or different, are

(a) aryl,

(b) alkoxy containing 1-4 carbon atoms,

(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part,

(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part,

(e) aryloxy,

(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or

(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms

R^{13} is (a) alkyl containing 1-4 carbon atoms, or

(b) alkylene containing 2-3 carbon atoms;

Z is $-O-$ or $-\overset{O}{\overset{\|}{C}}-$;

n is 0 or 1;

A is (a) alkylene containing 1-6 carbon atoms

(b) cycloalkylene containing 3-6 carbon atoms

(c) alkenylene containing 2-6 carbon atoms

(d) cycloalkenylene containing 3-6 carbon atoms, or

(e) alkynylene containing 2-6 carbon atoms;

D is (a) —CN

(b) $-\overset{O}{\overset{\|}{C}}-R^9$

(c) $-(Y)_m-(\overset{O}{\overset{\|}{C}})_r-R^{10}$

wherein

R^9 is (a) alk xy containing 1-5 carbon atoms, or

(b) dialkylamino containing 1-3 carb n atoms in the alkyl parts;

m is 0 or 1;

r is 0 or 1;

Y is (a) —O—

(b) —NH—

(c) $—NR^{10}—$;

R^{10} is (a) H

(b) alkyl containing 1-3 carbon atoms,

(c) arylalkyl containing 1-2 carbon atoms in the alkyl part, or

(d) aryl;

R^5 is (a) H or

(b) $—\overset{\overset{\displaystyle O}{\|}}{C}—R^{14}$;

wherein

R^{14} is (a) alkyl containing 1-6 carbon atoms,

(b) arylalkyl containing 1-2 carbon atoms in the alkyl part

(c) aryl

(d) alkoxy containing 1-4 carbon atoms

(e) arylalkoxy containing 1-2 carbon atoms in the alkyl part

(f) aryloxy

(g) amino

(h) mono- or dialkylamino containing 1-4 carbon atoms in the alkyl part(s)

(i) arylalkylamino containing 1-2 carbon atoms in the alkyl part

(j) arylamino;

R^6 and R^8, which are the same or different, are

(a) H or

(b) alkyl containing 1-5 carbon atoms;

R^7 is (a) H

(b) alkyl containing 1-8 carbon atoms

(c) alkoxy containing 1-8 carbon atoms

(d) alkenyloxy containing 2-5 carbon atoms

(e) alkynyloxy containing 2-5 carbon atoms

(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group

(g) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group

(h) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms

(i) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms

(j) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(k) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

(l) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

—CH=CH—CH=CH

$—O—(CH_2)_p—$

$—CH_2(CH_2)_p—$

—O—CH=CH—

—NH—CH=CH—

$—\underset{\underset{\displaystyle CH_3}{|}}{N}—CH=CH—$

wher in p is 2, 3 or 4 and the O and N atoms always are attached to position 4 in th pyridine ring;

and physi logically acceptabl salts of the compounds I wher in X is S;

with th provis s that

(a) n t m re than one of R^6, R^7 and R^8 is hydrogen,

(b) when X is SO, R^5 is H and R^6, R^7 and R^8 are selected only from hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then R^1, R^2, R^3 and R^4 cannot be selected only from alkyl groups, halogen, alkoxycarbonyl, alkoxy or alkanoyl,

(c) when X is S, R^5 is H, alkanoyl or alkoxycarbonyl, and R^6, R^7 and R^8 are selected only from hydrogen, methyl, ethyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then R^1, R^2, R^3 and R^4 cannot be selected only from alkyl groups, halogen, alkoxycarbonyl, alkoxy, alkanoyl, trifluormethyl, or NO_2,

(d) when X is SO, one of R^6, R^7 and R^8 is H and the other two of R^6, R^7 and R^8 are alkyl, and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then those radicals R^1, R^2, R^3 and R^4 which are not H cannot be selected only from alkyl, halogen, cyano, $—\overset{\overset{\displaystyle O}{\|}}{C}—$(alkoxy), (alkyl)$—O\overset{\overset{\displaystyle O}{\|}}{C}—$(alkyl—, alkoxy, hydroxyalkyl, CF_3, or (alkyl)$—\overset{\overset{\displaystyle O}{\|}}{C}—$,

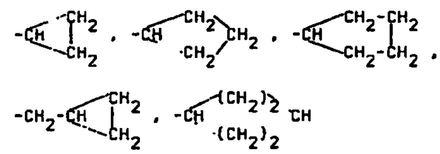
(e) when R^3, R^4, R^5 and R^{15} are H and simultaneously R^6 and R^8 are H or CH_3 and R^7 is OCH_3, then R^1 is not CF_3 when R^2 is H, and R^2 is not CF_3 when R^1 is H,

are effective as gastrointestinal cytoprotectives and as inhibitors of gastric acid secretion in mammals and man as stated above.

Illustrative examples of the various radicals in the formula I are as follows. These illustrative examples will be applicable to different radicals depending on the number of carbon atoms prescribed for each radical. It will be understood that the expressions "alkyl" and "alkoxy" include straight, branched and cyclic structures.

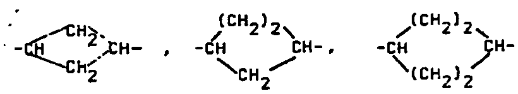
Halogen: F, Cl, Br, I

Alkyl: CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9, sec.-C_4H_9, iso.-C_4H_9, tert.-C_4H_9, n-C_5H_{11}, n-C_6H_{13},



Alkylene: $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-CH_2-CH(CH_3)-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$

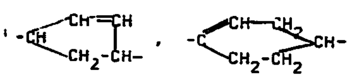
Cycloalkylene:



Alkenylene: $-CH{=}CH-$, $-CH_2-CH{=}CH-$, $-CH_2-CH{=}CH-CH_2-$, $-(CH_2)_2-CH{=}CH-CH_2-$, $-(CH_2)_3-CH{=}CH-CH_2-$

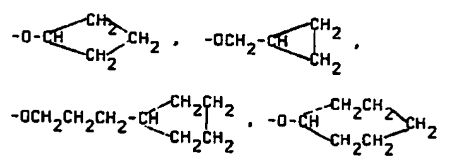
Alkylthio: $-S-CH_3$, $-S-C_2H_5$, $-S-i-C_3H_7$

Cycloalkenylene:



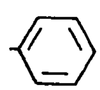
Alkynylene: $-C{\equiv}C-$, $-CH_2-C{\equiv}C-$,

Alkoxy: $-OCH_3$, $-OC_2H_5$, $-O-n-C_3H_7$, $-O-i-C_3H_7$, $-O-n-C_4H_9$, $-O-iso-C_4H_9$, $-O-sec.-C_4H_9$, $-O-tert.-C_4H_9$, $-O-n-C_5H_{11}$,

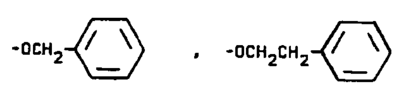


Alkoxyalkoxy: $-OCH_2OCH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OCH_2CH_3$, $-OCH_2CH_2CH_2OCH_2CH_2CH_3$

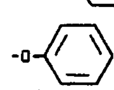
Aryl:



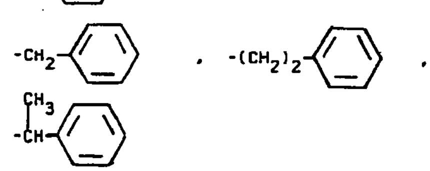
Arylalkoxy:



Aryloxy:



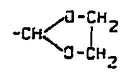
Arylalkyl:

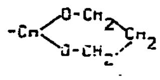


Alkenyloxy: $-O-CH{=}CH_2$, $-O-CH{=}CH-CH_3$, $-O-CH{=}CH-C_2H_5$, $-O-CH_2-CH{=}CH-CH_2CH_3$

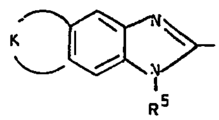
Alkynyloxy: $-O-C\equiv CH$, $-O-CH_2-C\equiv CH$, $-O-CH_2-C\equiv C-CH_3$
$-O-CH_2-C\equiv C-CH_2CH_3$

Illustrative examples of the radical $-CH(OR^{13})_2$ are:

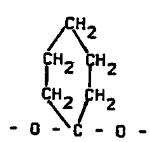
$-CH(OCH_3)_2$, $-CH(OC_2H_5)_2$, $-CH(OCH_2CH_2CH_3)_2$, ,



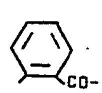
Illustrative examples of the ring structures involving R^1, R^2, R^3 or R^4 are

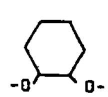


where K is
$-CH_2CH_2CH_2-$
$-CH_2CH_2CH_2CH_2-$
$-CH_2-C(CH_3)_2-CH_2-$
$-(CH_2)_5-$
$-CH=CH-CH=CH-$
$-CH(CH_3)-CH_2CH_2-$
$-CH_2-CH(CH_3)-CH_2-$
$-CH(CH_3)-CH(CH_3)-CH_2-CH_2-$
$-CH(CH_3)-CH(CH_3)-CH(CH_3)-CH(CH_3)-$
$-(CH_2)_2-NH-$
$-OCH_2O-$
$-OCH_2CH_2O-$
$-O-C(CH_3)_2-O-$
$-O(CH_2)_3O-$



$-CH_2-O-(CH_2)_2-O-$
$-CH_2-O-CH(CH_3)-CH_2-O-$





The radical $-(Z)_n-A-D$ comprises the following radicals.
The expression (alkyl 1-3C) etc. means alkyl groups containing 1, 2 or 3 carbon atoms.

A - CN

A - $\overset{O}{\overset{\|}{C}}$ - O -(alkyl 1-5c)

A - $\overset{O}{\overset{\|}{C}}$ - $N\begin{array}{l}\diagup\text{(alkyl 1-3c)}\\\diagdown\text{(alkyl 1-3c)}\end{array}$

A - H
A - (alkyl 1-3c)
A - (alkyl 1-2c)-aryl
A - aryl
A - O - H
A - O -(alkyl 1-3c)
A - O -(alkyl 1-2c)-aryl
A - O - aryl
A - NH - H
A - NH -(alkyl 1-3c)
A - NH -(alkyl 1-2c)-aryl
A - NH - aryl

A - $\overset{R^{10}}{\overset{|}{N}}$ - H

A - $\overset{R^{10}}{\overset{|}{N}}$ -(alkyl 1-3c)

A - $\overset{R^{10}}{\overset{|}{N}}$ -(alkyl 1-2c)-aryl

A - $\overset{R^{10}}{\overset{|}{N}}$ - aryl

A - O - $\overset{O}{\overset{\|}{C}}$ - H

A- O - $\overset{O}{\overset{\|}{C}}$ - (alkyl 1-3c)

A- O - $\overset{O}{\overset{\|}{C}}$ - (alkyl 1-2c)-aryl

A- O - $\overset{O}{\overset{\|}{C}}$ - aryl

A- NH - $\overset{O}{\overset{\|}{C}}$ - H

A- NH - $\overset{O}{\overset{\|}{C}}$ -(alkyl 1-3c)

A- NH - $\overset{O}{\overset{\|}{C}}$ -(alkyl 1-2c)-aryl

A- NH - aryl

A- $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ - H

A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ - (alkyl 1-3c)

A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ -(alkyl 1-2c)-aryl

A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ -aryl

-O -A - CN

-O -A - $\overset{O}{\overset{\|}{C}}$-O-(alkyl 1-5c)

-O -A - $\overset{O}{\overset{\|}{C}}$ - $N\begin{array}{l}\diagup\text{(alkyl 1-3c)}\\\diagdown\text{(alkyl 1-3c)}\end{array}$

-O-A - H
-O-A -(alkyl 1-3c)
-O-A-(alkyl 1-2c)-aryl
-O-A-aryl

-O - A - O - H
-O - A - O -(alkyl 1-3c)
-O - A - O -(alkyl 1-2c)-aryl
-O - A - O - aryl
-O - A - NH - H
-O - A - NH -(alkyl 1-3c)
-O - A - NH -(alkyl 1-2c)-aryl
-O - A - NH - aryl

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ - H

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ -(alkyl 1-3c)

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ -(alkyl 1-2c)-aryl

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ - aryl

-O - A - O - $\overset{O}{\overset{\|}{C}}$ - H

-O - A - O- $\overset{O}{\overset{\|}{C}}$ - (alkyl 1-3c)

-O - A - O- $\overset{O}{\overset{\|}{C}}$ - (alkyl 1-2c)-aryl

-O - A - O- $\overset{O}{\overset{\|}{C}}$ - aryl

-O - A - NH - $\overset{O}{\overset{\|}{C}}$ - H

-O - A - NH - $\overset{O}{\overset{\|}{C}}$ -(alkyl 1-3c)

-O - A - NH - $\overset{O}{\overset{\|}{C}}$ -(alkyl 1-2c)-aryl

-O - A - NH - aryl

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ - H

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ - (alkyl 1-3c)

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ -(alkyl 1-2c)-aryl

-O - A - $\overset{R^{10}}{\overset{|}{N}}$ - $\overset{O}{\overset{\|}{C}}$ -aryl

-$\overset{O}{\overset{\|}{C}}$- A -CN

-$\overset{O}{\overset{\|}{C}}$- A -$\overset{O}{\overset{\|}{C}}$ - O-(alkyl 1-5c)

-$\overset{O}{\overset{\|}{C}}$- A -$\overset{O}{\overset{\|}{C}}$ - $N\begin{array}{l}\diagup\text{(alkyl 1-3c)}\\\diagdown\text{(alkyl 1-3c)}\end{array}$

-$\overset{O}{\overset{\|}{C}}$ -A -H

-$\overset{O}{\overset{\|}{C}}$ -A -(alkyl 1-3c)

-$\overset{O}{\overset{\|}{C}}$ -A -(alkyl 1-2c)-aryl

-$\overset{O}{\overset{\|}{C}}$ -A- aryl

-C(=O)-A-O-H

-C(=O)-A-O-(alkyl 1-3c)

-C(=O)-A-O-(alkyl 1-2c)-aryl

-C(=O)-A-O-aryl

-C(=O)-A-NH-H

-C(=O)-A-NH-(alkyl 1-3c)

-C(=O)-A-NH-(alkyl 1-2c)-aryl

-C(=O)-A-NH-aryl

-C(=O)-A-N(R^{10})-H

-C(=O)-A-N(R^{10})-(alkyl 1-3c)

-C(=O)-A-N(R^{10})-(alkyl 1-2c)-aryl

-C(=O)-A-N(R^{10})-aryl

-C(=O)-A-O-C(=O)-H

-C(=O)-A-O-C(=O)-(alkyl 1-3C)

-C(=O)-A-O-C(=O)-(alkyl 1-2C)-aryl

-C(=O)-A-O-C(=O)-aryl

-C(=O)-A-NH-C(=O)-H

-C(=O)-A-NH-C(=O)-(alkyl 1-3C)

-C(=O)-A-NH-C(=O)-(alkyl 1-2C)-aryl

-C(=O)-A-NH-aryl

-C(=O)-A-N(R^{10})-C(=O)-H

-C(=O)-A-N(R^{10})-C(=O)-(alkyl 1-3C)

-C(=O)-A-N(R^{10})-C(=O)-(alkyl 1-2C)-aryl

-C(=O)-A-N(R^{10})-C(=O)-aryl

The radical -C(=O)-R^{11} comprises the following radicals.

-C(=O)-aryl

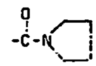
-C(=O)-O-(alkyl 1-4C)

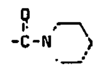
-C(=O)-O-(alkyl 1-3 c)-O-(alkyl 1-3c)

-C(=O)-O-(alkyl 1-2c)-aryl

-C(=O)-O-aryl

-C(=O)-N(alkyl 1-3c)(alkyl 1-3c)

 (optionally substituted with alkyl)

 (optionally substituted with alkyl)

The radical -O-C(=O)-R^{12} comprises the following radicals.

-O-C(=O)-aryl

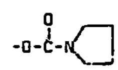
-O-C(=O)-O-(alkyl 1-4c)

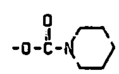
-O-C(=O)-O-(alkyl 1-3c)-O-(alkyl 1-3c)

-O-C(=O)-(alkyl 1-2c)-aryl

-O-C(=O)-O-aryl

-O-C(=O)-N(alkyl 1-3c)(alkyl 1-3c)

 (optionally substituted with alkyl)

 (optionally substituted with alkyl)

The radical -C(=O)-R^{14} comprises the following radicals:

-C(=O)-(alkyl 1-6c)

-C(=O)-(alkyl 1-2c)-aryl

-C(=O)-aryl

-C(=O)-O-(alkyl 1-4c)

-C(=O)-O-(alkyl 1-2c)-aryl

-C(=O)-O-aryl

-C(=O)-NH_2

-C(=O)-NH(alkyl 1-4c)

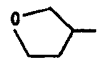
-C(=O)-N(alkyl 1-4c)(alkyl 1-4c)

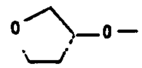
-C(=O)-N(alkyl 1-2c)(aryl)

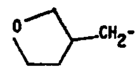
-C(=O)-NH(aryl)

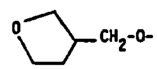
Further illustrative examples of the radicals in the formula I are:

alkylsulfinyl: $SOCH_3$, SOC_2H_5, $SOCH_2CH_2CH_3$, SO-i-C_3H_7, SO-n-C_4H_9, SO-n-C_5H_{11}

oxacycloalkyl: 

oxacycloalkoxy: 

oxacycloalkyl-alkyl: 

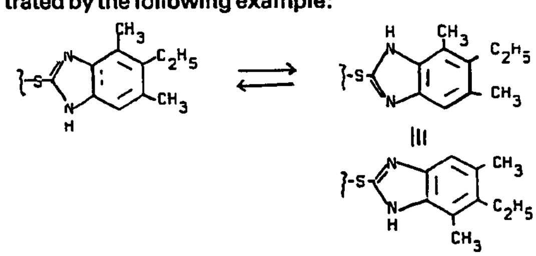
oxacycloalkyl-alkoxy: 

The compounds of the invention that are sulfoxides (X=SO) have an asymmetric centre in the sulfur atom, i.e. these compounds exist as two optical isomers (enantiomers), or if they also contain one or more asymmetric carbon atoms the compounds have two or more diastereomeric forms, each existing in two enantiomeric forms. Such asymmetric carbon atoms may be the carbon atom on which R^{15} is attached (when R^{15} is other than H) or a carbon atom in some of the substituents.

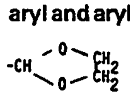
Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixture of the two are within the scope of the present invention. It should be understood that all the diastereomeric forms possible (pure enantioners or racemic mixtures) are within the scope of the invention.

The compounds of the invention that are sulfides (X=S) may be asymmetric due to one or more asymmetric carbon atoms, as described above. The different diasetereomeric forms possible as well as the pure enantiomers and racemic mixtures are within the scope of the invention.

It should be noted that for all the compounds of the invention wherein R^5 is H the substituents R^1 and R^4 as well as R^2 and R^3 are considered to be equivalent. This is due to the tautomerism in the imidazole part of the benzimidazole nucleus causing an equilibrium between the two possible NH-forms. This is illustrated by the following example:

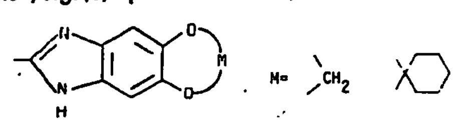


I Preferred groups of the radicals R^1, R^2, R^3 and R^4 are:

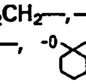
1. H
2. halogens F, Cl, Br and the groups CN, CHO, CO(aryl), COO(alkyl), CF_3, SCH_3, $SOCH_3$ and NO_2
3. the groups alkylene-D, O-alkylene-D and CO-alkylene-D wherein D is CN, COO(alkyl), COR^{10}, OR^{10} and R^{10}
4. aryl and aryloxy
5. 
6. $—CH_2CH_2CH_2—$, $—CH_2CH_2CH_2CH_2—$ and $—CH=CH—CH=CH—$
7. $—CH=CH—CH=\overset{|}{C}—(CH_2)_{2-3}—$
8. saturated heterocyclic ring structures having 2 oxygen atoms.
9. unsaturated 6-membered heterocyclic ring structures having one nitrogen atom

II Further preferred groups of the radicals R^1, R^2, R^3 and R^4 are:

1. H
2. halogens Cl and Br and the groups CO(phenyl), $COOCH_3$, CF_3, SCH_3 and $SOCH_3$
3. the groups alkyl, alkoxyalkyl, aryloxyalkyl, arylalkyl, aryl
4. the groups alkoxy, alkoxyalkoxy, aryloxyalkoxy, arylalkoxy, aryloxy
5. the group alkanoyl
6. $—CH_2CH_2CH_2—$, $—CH_2CH_2CH_2CH_2—$ and $—CH=CH—CH=CH—$
7. $—CH=CH—CH=\overset{|}{C}—(CH_2)_{2-3}—$
8. saturated heterocyclic ring structures having 2 oxygen atoms in 4,5-, 5,6- or 6,7-"catechol positions", e.g. (5,6-position shown)



III Still further preferred groups of the radicals R^1, R^2, R^3 and R^4 are:

1. H
2. Br and the groups $COOCH_3$ and CF_3
3. the groups CH_3, C_2H_5, $CH(CH_3)_2$, $CH_3OCH_2CH_2—$, phenyl
4. the groups CH_3O, $CH_3(CH_2)_6O—$, $CH_3OCH_2CH_2O—$, (phenyl)-$OCH_2CH_2CH_2O—$, (phenyl)$CH_2CH_2O—$, (phenyl)O—
5. the groups $CH_3CO—$, $C_2H_5CO—$
6. $—CH_2CH_2CH_2—$, $—CH_2CH_2CH_2CH_2—$
7. $—OCH_2O—$,  in the 5,6-"catechol position"

IV Particularly pref rred groups f th radicals R^1, R^2, R^3 and R^4 are:
H, $COOCH_3$, CF_3, CH_3, C_2H_5, $CH(CH_3)_3$, CH_3O, $—CH_2CH_2CH_2—$, $—CH_2CH_2CH_2CH_2—$ and $—OCH_2O—$

V In a pref rr d embodiment, at least three of the radicals R^1, R^2, R^3 and R^4 are oth r than hydrogen, r

theyf rm at least one ring.

VI In another preferred embodiment the radicals R^1 and R^2 form a ring structur

VII In an ther preferred embodiment the radicals R^2 and R^3 form a ring structure.

VIII In a preferred embodiment at least three of the radicals R^1, R^2, R^3 and R^4 are other than hydrogen.

IX In a preferred embodiment the radicals R^1, R^2, R^3 and R^4 are selected from H, halogen, CF_3, alkyl and alkoxy groups.

X In a preferred embodiment the radicals R^1, R^2, R^3 and R^4 are selected from H, alkyl and alkoxy groups.

XI In a preferred embodiment the radicals R^1, R^2, R^3 and R^4 are selected from H and alkyl groups.

XII The preferred groups of X is S.

XIII The preferred group of X is SO.

XIV The preferred group of R^{15} is H.

XV Preferred groups of the radical R^5 are H, arylcarbonyl, alkoxycarbonyl, arylalkoxycarbonyl, dialkylaminocarbonyl and arylaminocarbonyl.

XVI Further preferred groups of the radical R^5 are H, phenylcarbonyl, methoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, dimethylaminocarbonyl and phenylaminocarbonyl.

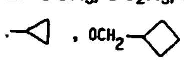
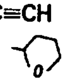
XVII Particularly preferred of the radical R^5 is H.

XVII Preferred groups of the radicals R^6 and R^8 are:

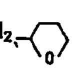
1. H, CH_3, C_2H25, C_3H_7 and $CH(CH_3)_2$
2. ring structures connecting position 4 in the pyridine ring.

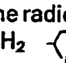
XIX Particularly preferred groups of the radicals R^6 and R^8 are H, CH_3, C_2H_5 and ring structures also connecting position 4 in the pyridine ring

XX Preferred groups of the radical R^7 are:

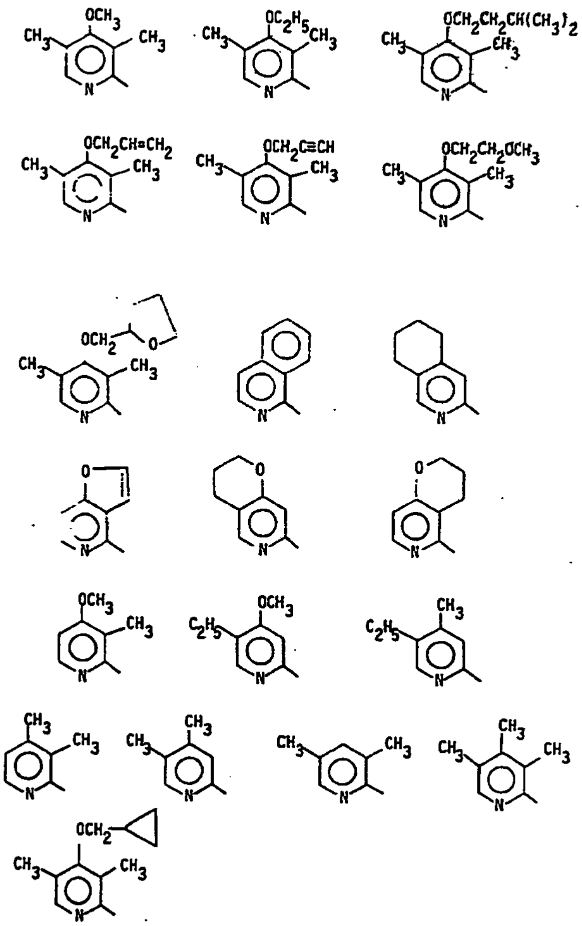
1. H, CH_3, C_2H_5
2. OCH_3, OC_2H_5, $OCH_2CH_2CH_3$, $O(CH_2)_3CH_3$, OCH_2 
3. $OCH_2CH{=}CH_2$, $OCH_2C{\equiv}CH$
4. $OCH_2CH_2OCH_3$, OCH_2 
5. $OCH_2CH_2N(CH_3)_2$
6. —CH=CH—CH=CH-bound to positions 3 and 4, —CH=CH—CH=CH-bound to positions 4 and 5, —$CH_2CH_2CH_2$-bound to positions 3 and 4, —$CH_2CH_2CH_2$-bound to positions 4 and 5, —$CH_2CH_2CH_2CH_2$-bound to positions 3 and 4, —$CH_2CH_2CH_2CH_2$-bound to positions 4 and 5, —OCH_2CH_2-bound to positions 3 and 4, —OCH_2CH_2-bound to positions 4 and 5, —$OCH_2CH_2CH_2$-bound to positions 3 and 4, —$OCH_2CH_2CH_2$-bound to positions 4 and 5,

XXI Further preferred groups of the radical R^7 are:

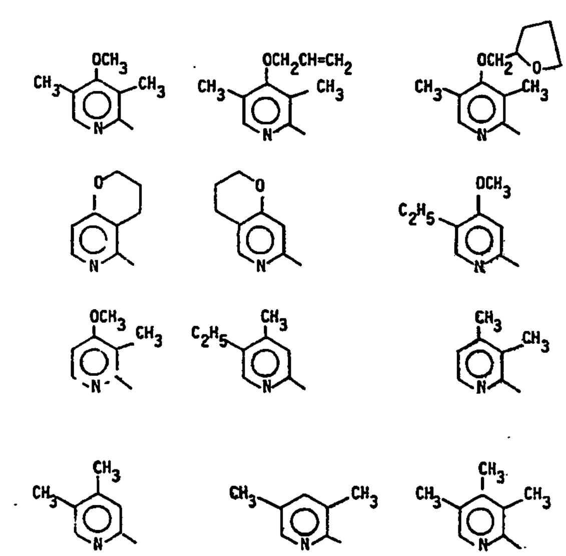
1. CH_3
2. OCH_3, OC_2H_5, $OCH_2CH_2CH(CH_3)_2$
3. $OCH_2CH{=}CH_2$
4. $OCH_2CH_2OCH_3$, OCH_2 
5. —$CH_2CH_2CH_2$-b und to positions 3 and 4, —$CH_2CH_2CH_2$-bound to p sitions 4 and 5, —$CH_2CH_2CH_2CH_2$-bound to positions 3 and 4, —$CH_2CH_2CH_2CH_2$-bound to positions 4 and 5, —OCH_2CH_2-bound to positions 3 and 4, —OCH_2CH_2-bound to positions 4 and 5, —$OCH_2CH_2CH_2$-bound to positions 3 and 4, —$OCH_2CH_2CH_2$-bound to positions 4 and 5.

XXII Particularly preferred groups f the radical R^7 are CH_3, OCH_3, $OCH_2CH_2CH(CH_3)_2$, —OCH_2 , —$OCH_2CH_2CH_2$-b und to positions 3 and 4 or to positions 4 and 5.

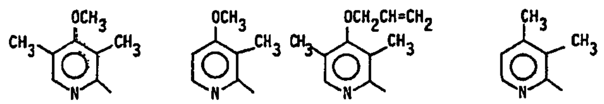
XXIII Preferred pyridyl substitution patterns are:



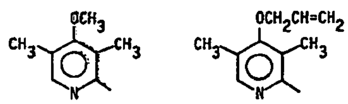
XXIV Further preferred pyridyl substitution patterns are:



XXV Still further preferred pyridyl substitution patterns ar :



XXVI Particularly preferred pyridyl substitution patterns are:

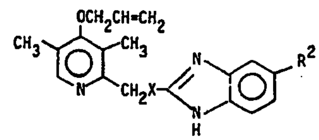


XXVII In a preferred embodiment two of the radicals R^6, R^7 and R^8 form one ring structure and the third radical of R^6, R^7 and R^8 is H.

XXVIII In a preferred embodiment R^{15} and R^5 are H, at least three times of the radicals R^1, R^2, R^3 and R^4 are other than H, R^6 and R^8 are H or CH_3 and R^6 is CH_3, OCH_3 r $OCH_2CH{=}CH_2$.

XXIX In a preferred mbodiment R^{15} and R^5 are H, the radicals R^1, R^2, R^3 and R^4 form at least one ring structure, R^6 and R^8 are H or CH_3 and R^7 is CH^3, OCH^3 or $OCH_2CH{=}CH_2$.

XXX Preferred compounds are those of the formula



wherein R^2 is alkyl or alkoxy, preferably CH_3, C_2H_5, $CH(CH_3)_2$ and OCH_3, and X is S or SO.

Further illustrative examples of the radicals in the formula I are given in the examples and lists of specific compounds given elsewhere in this specification.

Illustrative examples of compounds included in the scope of the invention are given in the following Table 1.

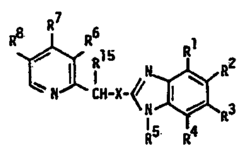


Table 1
Illustrative examples of compounds included in the scope of the invention.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3
SO	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3

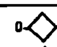
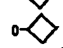
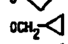
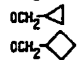
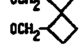
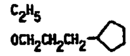
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	CH_3	CH_3	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	H	CH_3	CH_3	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	H	CH_3	CH_3	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	CH_3	H	H	CH_3	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	CH_3	H	H	CH_3	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	CH_3	H	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	CH_3	H	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	H	CH_3	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	H	CH_3	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	H	OCH_3	H	H	H	CH_3	$OCH_2C\equiv CH$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2C\equiv CH$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$O(CH_2)_3CH=CH_2$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$O(CH_2)_3CH_3$	CH_3
S	H	H	OCH_3	H	H	H	CH_3	$OCH(CH_3)_2$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$OCH(CH_3)_2$	CH_3
S	H	H	OCH_3	H	H	H	CH_3	$OC(CH_3)_3$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$OC(CH_3)_3$	CH_3

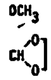
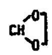
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	H	OCH_3	H	H	H	CH_3		CH_3
SO	H	H	OCH_3	H	H	H	CH_3		CH_3
S	H	H	OCH_3	H	H	H	CH_3		CH_3
SO	H	H	OCH_3	H	H	H	CH_3		CH_3
S	H	H	OCH_3	H	H	H	CH_3		CH_3
SO	H	H	OCH_3	H	H	H	CH_3		CH_3
S	H	H	OCH_3	H	H	H	CH_3	$O(CH_2)_2N(CH_3)_2$	CH_3
S	H	H	OCH_3	H	H	H	CH_3	$O(CH_2)_2\overset{\oplus}{N}H(CH_3)_2Cl^{\ominus}$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$O(CH_2)_2N(CH_3)_2$	CH_3
S	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3
SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3
SO	H	H	OCH_3	H	H	H	H	OCH_3	C_2H_5
S	H	H	OCH_3	H	H	H	H	$O(CH_2)_3CH_3$	C_2H_5
SO	H	H	OCH_3	H	H	H	H	$O(CH_2)_3CH_3$	C_2H_5
SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH_2CH_2CH(CH_3)_2$	CH_3
SO	H	CH_3	OCH_3	CH_3	H	H	H	C_2H_5	CH_3
SO	H	H	OCH_3	H	H	H	CH_3		CH_3
SO	H	CH_3	OCH_3	CH_3	H	H	H	$CH(CH_3)_2$	CH_3

cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	H	OCH_3	H	H	H	H	$-(CH_2)_4-$	
SO	H	H	OCH_3	H	H	H	H	$-(CH_2)_4-$	
S	H	H	OCH_3	H	H	H	$-(CH_2)_4-$		H
SO	H	H	OCH_3	H	H	H	$-(CH_2)_4-$		H
S	H	H	OCH_3	H	H	H	H	$-O-(CH_2)_3-$	
SO	H	H	OCH_3	H	H	H	H	$-O-(CH_2)_3-$	
S	H	H	OCH_3	H	H	H	$-(CH_2)_2-O-$		H
SO	H	H	OCH_3	H	H	H	$-(CH_2)_2-O-$		H
S	H	H	OCH_3	H	H	H	H	-CH=CH-CH=CH-	
SO	H	H	OCH_3	H	H	H	H	-CH=CH-CH=CH-	
S	H	H	OCH_3	H	H	H	-CH=CH-CH=CH-		H
SO	H	H	OCH_3	H	H	H	-CH=CH-CH=CH-		H
S	H	H		H	H	H	CH_3	OCH_3	CH_3
SO	H	H		H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH(OCH_3)_2$	H	H	H	CH_3	OCH_3	CH_3

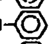
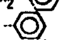
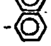
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H	$CH(OCH_3)_2$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CHO	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	CHO	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH=CH-COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH=CH-COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2CON(CH_3)_2$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2CON(CH_3)_2$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CH=CH-CN	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	CH=CH-CN	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CH_2CH_2CN	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	CH_2CH_2CN	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2CH_2OH$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2CH_2OH$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2CH_2OCOCH_3$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2CH_2OCOCH_3$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2CH_2N(CH_3)_2$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2CH_2N(CH_3)_2$	H	H	H	CH_3	OCH_3	CH_3

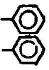
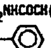
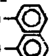
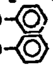
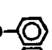
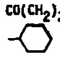
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	H	$CH_2CH_2CH_2NHCOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2CH_2NHCOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH{=}CH{-}COCH_3$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH{=}CHCOCH_3$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH{=}CH-$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH{=}CH-$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CH_2CH_2-	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	CH_2CH_2-	H	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	H	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	CH_3	H	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	H	CH_2-	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	CH_2-	H	H	H	CH_3	OCH_3	CH_3
S	H	H	O-	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	O-	H	H	H	CH_3	OCH_3	CH_3
S	H	H	OCH_2CH_2 	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	OCH_2CH_2 	H	H	H	CH_3	OCH_3	CH_3

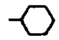
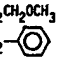
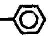
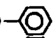
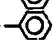
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	H	OCH_2CN	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	OCH_2CN	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$OCH_2COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$OCH_2COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	OCH_2CH_2OH	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	OCH_2CH_2OH	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$OCH_2CH_2OCOCH_2-$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$OCH_2CH_2OCOCH_2-$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$OCH_2CH_2NH_2$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$OCH_2CH_2NH_2$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$OCH_2CH_2NHCOCH(CH_3)_2$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$OCH_2CH_2NHCOCH(CH_3)_2$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	OCH_2CO-	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	OCH_2CO-	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CO-	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	CO-	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CO(CH_2)_3O-$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CO(CH_2)_3O-$	H	H	H	CH_3	OCH_3	CH_3
S	H	H		H	H	H	CH_3	OCH_3	CH_3

cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H		H	H	H	CH_3	OCH_3	CH_3
S	H	H	$COOCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	H	$COOCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	H	$COOCH_2$– 	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	H	$COOCH_2$– 	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	H	CH_2OH	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	H	CH_2OH	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	H	CH_2OCO– 	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	H	CH_2OCO– 	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	H	$COOCH_3$	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	H	$COOCH_3$	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	H	$CH_2CH_2OCH_3$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2OCH_3$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH(CH_3)_2$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	H	$CH(CH_3)_2$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	H	$C(CH_3)_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	H	$C(CH_3)_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	CH_3	OCH_3	CH_3	H	H	CH_3	OCH_3	CH_3

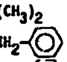
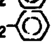
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	CH_3	OCH_3	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	OCH_3	CH_3	H	H	CH_3	CH_3	H
SO	H	CH_3	OCH_3	CH_3	H	H	CH_3	CH_3	H
S	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	H	CH_3	CH_3
SO	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	H	CH_3	CH_3
S	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	H	CH_3
SO	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	H	CH_3
S	H	CH_3	COC_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	COC_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3
S	CH_3	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3
SO	CH_3	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	CH_3
S	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3

cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	H
SO	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	H
S	H	CH_3	$CH(CH_3)_2$	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	$CH(CH_3)_2$	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	$CH(CH_3)_2$	CH_3	H	H	CH_3	CH_3	CH_3
SO	H	CH_3	$CH(CH_3)_2$	CH_3	H	H	CH_3	CH_3	CH_3
S	H	CH_3	$COCH_2$- 	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	$COCH_2$- 	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	OCH_3	Br	OCH_3	H	H	CH_3	OCH_3	CH_3
SO	H	OCH_3	Br	OCH_3	H	H	CH_3	OCH_3	CH_3
S	H	OCH_3	Br	OCH_3	H	H	CH_3	CH_3	H
SO	H	OCH_3	Br	OCH_3	H	H	CH_3	CH_3	H
S	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OCH_3	CH_3
SO	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OCH_3	CH_3
S	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OC_2H_5	CH_3
SO	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OC_2H_5	CH_3
S	H	CH_3	OCH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3

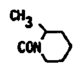
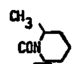
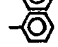
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	CH_3	OCH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
S	H	CH_3	OCH_3	H	CH_3	H	CH_3	OCH_3	CH_3
SO	H	CH_3	OCH_3	H	CH_3	H	CH_3	OCH_3	CH_3
S	H	Cl	OCH_3	H	OCH_3	H	CH_3	OCH_3	CH_3
SO	H	Cl	OCH_3	H	OCH_3	H	CH_3	OCH_3	CH_3
S	H	Cl	Cl	Cl	H	H	CH_3	OCH_3	CH_3
SO	H	Cl	Cl	Cl	H	H	CH_3	OCH_3	CH_3
S	H	Cl	Cl	Cl	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	Cl	Cl	Cl	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	Cl	Cl	Cl	Cl	H	CH_3	OCH_3	CH_3
SO	H	Cl	Cl	Cl	Cl	H	CH_3	OCH_3	CH_3
S	H	Cl	Cl	Cl	Cl	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	Cl	Cl	Cl	Cl	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	OCH_3	Br	H	OCH_3	H	CH_3	OCH_3	CH_3
SO	H	OCH_3	Br	H	OCH_3	H	CH_3	OCH_3	CH_3
S	H	OCH_3	Cl	Cl	OC_2H_5	H	CH_3	OCH_3	CH_3
SO	H	OCH_3	Cl	Cl	OC_2H_5	H	CH_3	OCH_3	CH_3
S	H	OCH_3	Cl	Cl	OC_2H_5	H	CH_3	CH_3	H

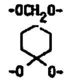
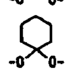
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	OCH_3	Cl	Cl	OC_2H_5	H	CH_3	CH_3	H
S	H	$COCH_3$	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
SO	H	$COCH_3$	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
S	H	F	Cl	H	Cl	H	CH_3	OCH_3	CH_3
SO	H	F	Cl	H	Cl	H	CH_3	OCH_3	CH_3
S	H	Cl	CH_2COOCH_3	Cl	H	H	CH_3	OCH_3	CH_3
SO	H	Cl	CH_2COOCH_3	Cl	H	H	CH_3	OCH_3	CH_3
S	H	Cl	CH_2CN	Cl	H	H	CH_3	OCH_3	CH_3
SO	H	Cl	CH_2CN	Cl	H	H	CH_3	OCH_3	CH_3
SO	H	-CH=CH-CH=CH-		-CH=CH-CH=CH-		H	CH_3	OCH_3	CH_3
S	H	H		H	H	H	CH_3	OCH_3	CH_3
SO	H	H		H	H	H	CH_3	OCH_3	CH_3
S	H	H		H	H	H	CH_3	OCH_3	CH_3
SO	H	H		H	H	H	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	H	CH_3	OCH_3	CH_3

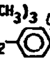
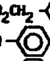
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H	$-OCH_2O-$		H	H	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	H	CH_3	CH_3	CH_3
SO	H	H	$-OCH_2O-$		H	H	CH_3	CH_3	CH_3
S	H	H			H	H	CH_3	OCH_3	CH_3
SO	H	H			H	H	CH_3	OCH_3	CH_3
S	H	-CH=CH-CH=N-		H	H	H	CH_3	OCH_3	CH_3
SO	H	-CH=CH-CH=N-		H	H	H	CH_3	OCH_3	CH_3
S	H	-CH=CH-CH=CH-		H	H	H	CH_3	OCH_3	CH_3
SO	H	-CH=CH-CH=CH-		H	H	H	CH_3	OCH_3	CH_3
S	H	H	-CH=CH-CH=CH-		H	H	CH_3	OCH_3	CH_3
SO	H	H	-CH=CH-CH=CH-		H	H	CH_3	OCH_3	CH_3
S	H	$-CH_2CH_2CH_2CH_2-$		H	H	H	CH_3	OCH_3	CH_3
SO	H	$-CH_2CH_2CH_2CH_2-$		H	H	H	CH_3	OCH_3	CH_3
S	H	OCH_3	$-CH_2CH_2CH_2-$		Cl	H	CH_3	OCH_3	CH_3
SO	H	OCH_3	$-CH_2CH_2CH_2-$		Cl	H	CH_3	OCH_3	CH_3
S	H	OCH_3	$-CH_2CH_2CH_2-$		Cl	H	CH_3	OC_2H_5	CH_3

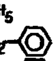
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	OCH_3	$-CH_2CH_2CH_2-$		Cl	H	CH_3	OC_2H_5	CH_3
S	H	$-CH=CH-CH=C-CH_2CH_2-$			H	H	CH_3	OCH_3	CH_3
SO	H	$-CH=CH-CH=C-CH_2CH_2-$			H	H	CH_3	OCH_3	CH_3
S	H	H	 CO-		H	H	CH_3	OCH_3	CH_3
SO	H	H	 CO-		H	H	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	CO_2CH_3	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	CO_2CH_3	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	$CO_2C_2H_5$	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	$CO_2C_2H_5$	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	$CO_2C(CH_3)_3$	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	$CO_2C(CH_3)_3$	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	CO_2CH_2- 	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	CO_2CH_2- 	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	CO- 	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	CO 	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	$CONH_2$	CH_3	OCH_3	CH_3

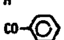
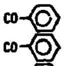
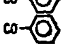
cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H	$-OCH_2O-$		H	$CONH_2$	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	$CONHC_2H_5$	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	$CONHC_2H_5$	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	$CONHCH_2-$ 	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	$CONHCH_2-$	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	CONH- 	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	CONH- 	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	$CON(CH_3)_2$	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	$CON(CH_3)_2$	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH_2OCH_3$	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH_2OCH_3$	CH_3
S	H	H	OCH_3	H	H	H	-CH=CH-O-		H
SO	H	H	OCH_3	H	H	H	-CH=CH-O-		H
S	H	H	OCH_3	H	H	H	H	-O-CH=CH-	
SO	H	H	OCH_3	H	H	H	H	-O-CH=CH-	
S	H	H	OCH_3	H	H	H	-CH=CH-NH-		H
SO	H	H	OCH_3	H	H	H	-CH=CH-NH-		H
S	H	H	OCH_3	H	H	H	H	-NH-CH=CH-	

cont.

cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H	OCH_3	H	H	H	H	-NH-CH=CH-	
S	H	H	OCH_3	H	H	H	$-CH=CH-N(CH_3)-$		H
SO	H	H	OCH_3	H	H	H	$-CH=CH-N(CH_3)-$		H
S	H	H	OCH_3	H	H	H	H	$-N(CH_3)-CH=CH-$	
SO	H	H	OCH_3	H	H	H	H	$-N(CH_3)-CH=CH-$	
S	H	CH_3	$CH_2C\equiv CH$	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	$CH_2C\equiv CH$	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH_2CH_2CH_2O$- 	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$CH_2CH_2CH_2O$- 	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$OCH_2CH_2CH_2O$- 	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$OCH_2CH_2CH_2O$- 	H	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	$O(CH_2)_6CH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	$O(CH_2)_6CH_3$	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	H	C_2H_5	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	H	C_2H_5	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	H	OCH_3	H	H	CO- 	CH_3	OCH_3	CH_3
S	H	H	H	OCH_3	H	CO- 	CH_3	OCH_3	CH_3
SO	H	H	OCH_3	H	H	CO- 	CH_3	OCH_3	CH_3

cont.

cont.

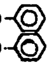
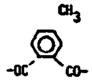
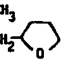
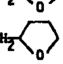
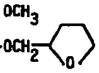
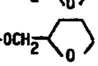
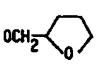
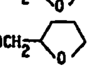
X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H	H	OCH_3	H	CO- 	CH_3	OCH_3	CH_3
S	H	H	CH_3	CH_2OCO- 	H	CO- 	CH_3	OCH_3	CH_3
S	H	H	CH_2OCO- 	CH_3	H	CO- 	CH_3	OCH_3	CH_3
S	H	H	$-OCH_2O-$		H	COC_2H_5	CH_3	OCH_3	CH_3
SO	H	H	$-OCH_2O-$		H	COC_2H_5	CH_3	OCH_3	CH_3
SO	H	H	CH_3	CH_3	H	$COOCH_3$	CH_3	OCH_3	CH_3
S	H			H	H	H	CH_3	OCH_3	CH_3
SO	H			H	H	H	CH_3	OCH_3	CH_3
S	H	H	SCH_3	H	H	H	CH_3	OCH_3	CH_3
S	H	H	$CH(CH_3)_2$	H	H	H	CH_3	OCH_2- 	CH_3
SO	H	H	$CH(CH_3)_2$	H	H	H	CH_3	OCH_2- 	CH_3
S	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	H	CH_3	CH_3	H	$COOC(CH_3)_3$	CH_3	OCH_3	CH_3

Table 1 cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	H	CH_3	CH_3	H	$CON(CH_3)_2$	CH_3	OCH_3	CH_3
SO	H	H	CH_3	CH_3	H	$CON(CH_3)_2$	CH_3	OCH_3	CH_3
S	H	H	Br	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
SO	H	H	Br	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	H
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	H
S	H	CH_3	CH_3	CH_3	H	H	H	CH_3	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	H	CH_3	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	H	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	H	CH_3
S	H	CH_3	CH_3	H	CH_3	H	CH_3	CH_3	H
SO	H	CH_3	CH_3	H	CH_3	H	CH_3	CH_3	H
S	H	CH_3	CN	CH_3	H	H	CH_3	OC_2H_5	CH_3
SO	H	CH_3	CN	CH_3	H	H	CH_3	OC_2H_5	CH_3
SO	H	H	$COOCH_3$	CH_3	H	H	H	OCH_3	C_2H_5
S	H	H	$-CH_2CH_2CH_2-$		H	H	CH_3	OCH_3	CH_3

Table 1 cont.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
SO	H	H	$-CH_2CH_2CH_2-$		H	H	CH_3	OCH_3	CH_3
SO	H	H	OCH_3	H	H	H	$-CH_2CH_2CH_2O-$		H
SO	H	H	OCH_3	H	H	H	H	$-OCH_2CH_2-$	
S	H	H	$SOCH_3$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	$SOCH_3$	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CH_3	CH_3	H	H	CH_3	$-OCH_2$	CH_3
SO	H	H	CH_3	CH_3	H	H	CH_3	$-OCH_2$	CH_3
S	H	$-CH{=}CH-CH{=}CH-$		$-CH{=}CH-CH{=}CH-$		H	CH_3	OCH_3	CH_3
SO	H	H	NO_2	H	H	H	CH_3	OCH_3	CH_3
S	H	H	CF_3	H	H	H	CH_3	OCH_2	CH_3
SO	H	H	CF_3	H	H	H	CH_3	OCH_2	CH_3
S	H	H	$CH_2CH_2COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3
SO	H	H	OCH_3	H	H	$\overset{O}{\|\|}C-OC(CH_3)_3$	CH_3	OCH_3	CH_3
SO	H	H	CH_3	CH_3	H	H	H	OCH_3	C_2H_5

The invention takes into consideration that compounds that structurally deviate from the formula I, after administration to a living organism may be transformed to a compound of formula I and in this structural form exert their effect. Such compounds structurally deviating from compounds of the formula I, are included in the scope of the invention.

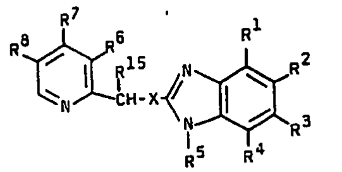
Likewise, certain compounds of formula I may be metabolized into ther comp unds of formula I before exerting their ff ct. Compounds of the inventi n wherein X is S are thus believed to exert their antisecr t ry and cyt protective activities after m tab lism to compounds wherein X is SO and compounds of the invention wherein R^5 is $R^{14}CO$ are believed to exert antis cretory and cyt protectiv activity after metabolism to compounds wh rein R^5 is H. These considerations are also a further aspect of the invention.

Further, it is believed that all compounds of formula I wherein X is SO after administration to a living organism, exert their antisecretory and cytoprotective effects after metabolic or pure chemical transformation to another, reactive species. Accordingly, the same is true also for the compounds of formula I wherein X is S, but via initial transformation to the corresponding compounds ff rmula I wher - in X is SO. These consid rations as well as such reactiv species per se are included within the scop of the pres nt inventi n.

Preparation

Comp unds of formula I abov may be prepared according t the following m thods:

a) Oxidizing a comp und of the formula I,

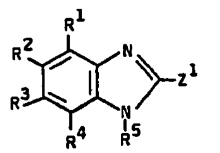


I

wherein X is S and R^{15}, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 have the meanings given, to give a compound of the same formula I wherein X is SO. This oxidation may be carried out by using an oxidizing agent selected from the group consisting of nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, l-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

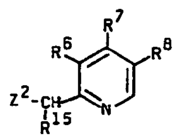
The oxidation may also be carried out enzymatically by using an oxidating anzyme or microbiotically by using a suitable microorganism.

b) Reacting a compound of the formula



II

with a compound of the formula



III

in which formulas R^{15}, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined previously and wherein one of Z^1 and Z^2 is SH and the other is a leaving group, gives a compound of the formula I wherein X is S.

Examples of leaving groups Z^1 and Z^2 in the compounds II and III are halogens, preferably chlorine, bromine or iodinem acyloxy radicals, for example residues of strong organic sulfonic acids, for instance of an arylsufonic acid, for example tosyloxy or an alkylsulfonic acid, for example mesyloxy, alkylmercapto groups, for example methylmercapto, alkylsulfinyl groups, for example methylsulfinyl and the like.

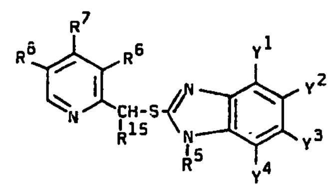
Thus, Z^1 or Z^2 when designating leaving groups may be a reactive esterified hydroxy group. The esterification may be carried out with an organic acid or with an inorganic acid such as HCl, HBr or H_2SO_4.

The reaction of a compound of formula II abov with a comp und of formula III is conveniently carri d ut in the presence of a suitable solvent that is inert under th reaction c nditi ns utiliz d as describ d h reinafter. The reacti n may further b carried out in th presence of a suitabl base. Suitable bas s include, for example, inorganic bases such as sodium or potassium hydroxide, sodium or potassium alkoxide, sodium r potassium hydride and the like, organic bases such as t rtiary amines, for example triethylamin and th lik .

Suitabl s lvents for the above described r action include, for example, alcohols, preferably lower alkanols such as methanol and ethanol, mixtures of such alcohols with water, ethers, such as tetrahydrofuran, halogenated hydrocarbons, such as methylene chloride. Aprotic solvents such as ethers and halogenated carbons are necessary in the case of sodium and potassium hydride.

The reaction of the compounds of formulas II and III may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture. It is preferred to carry out the reaction, however, at a temperature at or close to the boiling point of the reaction mixture for the preparation of a compound of the formula I wherein R^5 is H.

c) Esterification of a compound of the formula

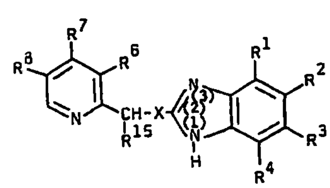


IV

wherein R^{15}, R^5, R^6, R^7 and R^8 are as defined above and Y^1, Y^2, Y^3 and Y^4 represent either R^1, R^2, R^3 and R^4 according to the above definition, respectively, or the groups $(Z)_n$-A-COOH, COOH and $(Z)_n$-A-OH, whereby Z, n and A are as defined above, by reaction with the appropriate alcohol R^9OH, $R^{10}OH$ or carboxylic acid $R^{10}COOH$, respectively, to the formation of a compound of formula I containing a radical R^1, R^2, R^3 and/or R^4 which is either of the ester groups $(Z)_n$-A-$COOR^9$, $COOR^{10}$ or $(Z)_n$-A-$OCOR^{10}$.

The esterfication is carried out as an ordinary esterfication, in the presence of an acid catalyst such as sulfuric acid, hydrochloric acid and p-toluenesulphonic acid and, if necessary, in the presence of an inert solvent such as toluene.

d) Acylation of a compound of the formula



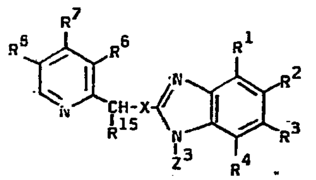
V

wherein R^{15}, X, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 are as defined above, by reaction with an appropriate acylating agent $(R^{14}CO)_2O$, $R^{14}COX^1$, whereby X^1 is a leaving group such as C1, N_3 and p-nitrophenoxy, R^aNCO, whereby R^a is defined by the relation R^aNH equals R^{14}, provided that R^a is K when R^{14} is amino, to the f rmation of a comp und of formula I wherein R^5 is $R^{14}CO$ as d fined abov .

The acylation is preferably carried out in the presence of a bas such as triethylamine, K_2CO_3 and NaOH and with a solvent such as tetrahydrofuran, acetonitrile and water. Normally, if the benzimidazole moiety is asymetrically substituted, b th th N(1)-

and the N(3)-acyl d rivatives are obtained, and therefore, if necessary, th two components have to be separated. This may b d ne by recrystallizati ns or by extractiv or chr matographic techniques.

) Hydrolyzing a compound of the formula



VI

wherein X, R^{15}, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 are as defined above and Z^3 is a suitable N-protecting group such as alkanoyl, carboalkoxy and trimethylsilyl, to the formation of a compound of the formula I wherein R^5 is H.

The alkanoyl group in Z^3 can have 1-6 carbon atoms and the carboalkoxy group 2-6 carbon atoms. The hydrolysis may be performed in alkaline solution or in acidic solution, the latter mainly for compounds wherein X is S;

whereafter the compound of the formula I obtained if desired, when X is -S-, is converted to a physiologically acceptable salt or oxidized to form a compound of the formula I wherein X is -SO-.

Depending on the process conditions and the starting materials, the end products of the formula I wherein X is S is obtained either as the free base or as a salt. The end products of the formula I wherein X is -SO- are obtained as the free base. Both the free base and the salts of these end products are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates. Acid addition salts of the new sulficides may in a manner known *per se* be transformed into free base using basic agents such as alkali or by ion exchange. The free bases of the sulfides obtained may also form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts.

Examples of such acids are hydrohalogen acids, sulfonic acid, phosphoric acid, nitric acid, and perchloric acid; aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, salicyclic acid or p-aminosalicylic acid, ambonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid, naphtylsulfonic acid or sulfanilic acids, methionine, tryptophane, lysine or arginine.

These or other salts of th new sulfide ompounds, as .g. picrates, may serv as purifying agents f the fre bases obtained. Salts of the bases may be form d, separated from solution, and then the free base can be recovered in higher purity from a new salt solution.

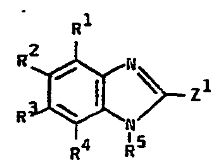
Rac mates obtained can b s parated according to known methods, .g. recrystallization fr m an optically active solvent, use of microorganisms, reactions with optically active acids forming diastere meric salts which can be separated, (e.g. separati n based on different solubilities of the diastereomers), acylation of the benzimidazole nitrogen (R^5 = H) or another nitrogen or oxygen atom in a substituent by an optically active activated carboxylic acid (e.g. acid chloride), followed by chromatographic separation and deacylation.

Suitable optically active acids for salt formation are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid, and for acylation O-methylmandelic acid. Preferably the more active part of the two antipodes is isolated.

In the case of diastereomeric mixtures (racemate mixtures) these may be separated into stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystallization.

The starting materials utilized in the processes a and c-e are obtained from the process b. The starting materials used for process b are in some cases known, but in most cases unknown. These unknown starting materials may, however, be obtained according to processes known *per se*.

Starting materials of the formula II



II

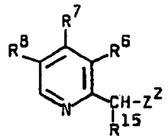
wherein Z^1 is SH may be obtained from the corresponding o-phenylenediamine by reaction with potassium ethylxanthate (Org. Synth. Vol. 30, p. 56) or thiophosgene.

The compounds of the formula II wherein Z^1 is alkylmercapto and alkylsulfinyl may be obtained from the above mentioned compound by simple S-alkylation with alkyl halide and by oxidation of the product from the S-alkylation, respectively.

The compounds of the formula II wherein Z^1 is halogen or acyloxy may be obtained from compounds of the same formula wherein Z^1 is OH by treatment with $POCl_3$, $POBr_3$ and the like or the appropriate acyl halide, respectively. The starting material wherein Z^1 is OH is obtained from the corresponding o-phenylenediamine by reaction with phosgene.

The o-phenylenediamines required may be obtained from the corresponding substituted benzenes according to processes known *per se*, e.g. by the consecutive processes: nitration, reduction, acetylation, nitration, deacetylati n and reduction, or from one of th intermediary stages just m nti ned. In order to obtain a o-phenylenediamine wherein R^5 is other than H, acylation (by th group $R^{14}CO$) is preferably mad on th nitro-aniline stage.

Starting materials of the formula

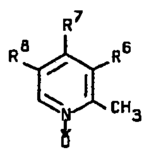


III

wherein R^{15} is H, may be obtained either from the correspondingly substituted (R^6, R^7 and R^8) 2 - methyl - substituted pyridine N - oxide via a known rearrangement to the intermediate 2 - pyridinylmethanol or via a hydroxymethylation of the substituted (R^6, R^7 and R^8) pyridine to give the same intermediate, and then treatment of the 2 - pyridinylmethanol with halogenating agents such as thionyl chloride or O - acylating agents such as p - toluenesulfonyl chloride to give compounds of the formula III wherein Z^2 is halogen and sulfonyloxy groups, respectively.

These leaving groups may then be substituted for alkylmercapto groups by treatment with e.g. sodium alkylmercaptide, which may then be oxidized to an alkylsulfinyl group, or substituted for SH by treatment with e.g. NaSH.

For the preparation of intermediates of formula

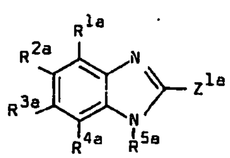


VII

wherein R^7 is alkoxy, alkenyloxy, alkynyloxy, alkoxyalkoxy and dialkylaminoalkoxy, a compound of formula VII, wherein R^7 is NO_2, is reacted by the corresponding sodium alkoxide. Analogously, for the preparation of an intermediate of formula VII wherein R^6 and R^7 or R^7 and R^8 form a ring structure including an oxygen atom at position 4, a compound of formula VII wherein R^7 is NO_2 and R^6 or R^8 represents hydroxyalkyl is reacted with a non-nucleophilic base.

The following intermediates A) and B) are included in the scope of the invention:

A) New compounds of the formula



VIII

wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and selected from the groups

(a) H,

(b) alkyl containing 1-6 carbon atoms, including cycloalkyl,

(c) alkoxyalkyl containing 1-3 carbon atoms in the alkoxy part and 1-6 carbon atoms in the alkyl part,

(d) aryloxyalkyl containing 1-6 carbon atoms in the alkyl part,

(e) arylalkyl containing 1-6 carb n atoms in th alkyl part,

(f) aryl,

(g) alkoxy containing 1-6 carbon atoms,

(h) alkoxyalkoxy containing 1-3 carbon atoms in the outer part and 1-6 carbon at ms in the part near st th aromatic ring,

(i) aryloxyalk xy containing 1-6 carb n atoms in the alkoxy part,

(j) arylalkoxy c ntaining 1-6 carbon at ms in the alkoxy part and

(k) aryloxy,

R^{5a} is

(a) H,

(b) alkoxycarbonyl containing 1-4 carbon atoms in the alkoxy part,

(c) arylalkoxycarbonyl containing 1-2 carbon atoms in the alkoxy part,

(d) dialkylaminocarbonyl containing 1-4 carbon atoms in each alkyl group, or

(e) arylaminocarbonyl,

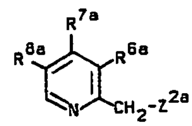
and Z^{1a} is

(a) SH,

(b) Cl or Br

and provided that not more than one of R^{1a}, R^{2a}, R^{3a} and R^{4a} is H, are suitable intermediates for the preparation of compounds of the formula I with R^1, R^2, R^3, R^4 and R^5 having the same meaning as R^{1a}, R^{2a}, R^{3a}, R^{4a} and R^{5a}, respectively, according to method b.

B) New compounds of the formula



IX

wherein R^{6a} and R^{8a} are

(a) H or

(b) alkyl containing 1-5 carbon atoms, and R^{7a} is

(a) alkenyloxy containing 2-5 carbon atoms, or

(b) alkynyloxy containing 2-5 carbon atoms,

(c) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms

(d) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms

(e) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(f) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms,

or

(g) R^{6a} and R^{7a}, or R^{7a} and R^{8a} together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a} is

—CH=CH—CH=CH—

—O—$(CH_2)_{pa}$—

—CH_2—$(CH)_{pa}$—

—O—CH=CH—

wherein pa is 2, 3 or 4 and the O atom always is attached to position R^{7a},

and Z^{2a} is

(a) SH,

(b) halogen Cl, Br, I or

(c) OH

and provided that not more than on of R^{6a} and R^{8a} is H, are suitable int rmediat s for the preparation of compounds of th formula I with R^6, R^7 and R^8 having the sam meaning as R^{6a}, R^{7a} and R^{8a}, resp ctively, according to method b.

For clinical use the compounds of the invention are formulated into pharmaceutical formulati ns for oral, rectal, parenteral r oth r m d f administrati n.

The pharmaceutical f rmulati n c ntains a c m- pound f th invention in combination with a pharmaceutically acceptable carrier. The carrier may be in th form of a solid, semi-solid or liquid dilu nt, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrer, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. Since the sulfoxides of the invention are susceptible to degradation in acid to neutral media, granules and tablets containing sulfoxides are preferably coated with an enteric coating which protects the active compound from acid degraduation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a v gatable oil, paraffin oil or other suitable vehicle f r gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro nema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may b prepared in the form of syrups or suspensi ns, e.g. solutions or suspensions containing from 0.2 % to 20 % by weight of the active ingr dient and the remaind r constisting of sugar or sugaralcohols and a mixture f ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1 % to 10 % by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extenporaneously before use.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Method a. Preparation of 4,6-dimethyl-5-methoxy-2-[[(3,4-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole.

m-Chloroperbenzoic acid, 91% (0.53 g. 0.0028 mol) dissolved in CH^2Cl^2 (25 ml) and cooled to −10°C was added under stirring to 4,6-dimethyl-5-methoxy-2-[[(3,4-dimethyl-2-pyridinyl) methyl] thio]-1*H*-benzimidazole (0.91 g, 0.0028 mol) dissolved in CH_2Cl_2 (50 ml) maintaining the temperature at −5°C. Stirring was continued at −5°C for 5 min and then NaOH (0.34 g, 0.0085 mol) dissolved in water (25 ml) was added under vigorous stirring. The two phases were separated and the aqueous phase was washed with CH_2Cl_2 (10 ml). More CH_2Cl_2 (50 ml) was added to the aqueous phase, the pH was adjusted to 9.5 by adding 2M HCl and after stirring the phases were separated. The organic phase was dried (Na_2SO_4), filtered and the solvent was evaporated off giving an oil which was crystallized from CH_3CN (15 ml) yielding the desired product (0.3 g, 32%), m.p. 161°C.

Example 2. Method a. Preparation of 4,6-dimethyl-5-heptyloxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole.

m-Chloroperbenzoic acid, 91% (1.13 g, 0.0059 mol) dissolved in CH_2Cl_2 (25 ml) and cooled to −10°C was added under stirring to 4,6-dimethyl-5-heptyloxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] thio]-1*H*-benzimidazole (2.7 g, 0.0059 m l) dissolved in CH_2Cl_2 (50 ml) maintaining the temperature at −5°C. Stirring was continued at −5°C for 10 min. The two phases were separated and then NaOH (0.26 g, 0.0066 mol) dissolved in water (50 ml) was add d under vigorous stirring. The tw phases were separated. The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated off giving a r sidual oil, which according to NMR included 30% of

unreacted starting material. The oil was chromatographed on a silica column using $CH_3OH—CH_2Cl_2$ 5:95 as eluant and then the product was recrystallized from CH_3CN giving the d sired product in crystalline form (0.85 g, 32%), m.p. 116°C.

Which one of these two procedures that have been used for the preparation of the different sulfoxides have been indicated in Table 2 below. For most of the compounds synthesized according to example 2 the chromatographic separation was not performed.

Example 3. Method b. Preparation of 4,6 - dimethyl - 5 - methoxy - 2 - [[(3,4 - dimethyl - 2 - pyridinyl) methyl] thio] - 1*H* - benzimidazole.

To 4,6 - dimethyl - 5 - methoxy - 2 - mercapto - 1*H* - benzimidazole (1.04 g, 0.0050 mol) in methanol (50 ml) were added (in the following order) NaOH (0.2 g, ;.0050 mol) dissolved in water (2 ml) and 3,4 - dimethyl - 2 - chloromethylpyridine hydrochloride (0.96 g, 0.0050 mol). The mixture was heated until reflux. NaOH (0.2 g, 0.0050 mol) dissolved in water (2 ml) was added dropwise and then the reflux was continued for 3 hours. The mixture was poured on ice-water (200 ml). Filtration and recrystallization from CH_3CN gave the desired product (1.1 g, 67%). NMR data for the final product is given below.

Example 4 and 5. Method d. Preparation of N[1] - benzoyl - 5 - methoxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) methyl] - thio] - 1*H* - benzimidazole and N[1] - benzoyl - 6 - methoxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) methyl] thio] - 1*H* - benzimidazole

5 - Methoxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) methyl] - thio] - 1*H* - benzimidazole (3.0 g, 0.009 mol) was dissolved in CH_3CN (30 ml) and triethylamine (1.9 ml) was added. Benzoyl chloride (1.4 g, 0.010 mol) was added dropwise under stirring during 15 min. Then the mixture was stirred at 55°C for 45 min. The solvent was evaporated off and ether was added to the residue under ice-cooling. The crystalline residue, thus obtained was stirred with water, filtered off and dried giving a white crystalline product mixture (1.9 g, 48%) of the desired two products in a 75:25 molar ratio (according to HPLC-analysis and NMR). NMR data for the final products is given below.

Example 6. Method d. Preparation of N - methoxycarbonyl - 5,6 - methylenedioxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) - methyl] sulfinyl] - 1*H* - benzimidazole.

Chloro methylformate (0.24 g, 0.0026 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of 5,6 - methylenedioxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) - methyl] sulfinyl] - 1*H* - benzimidazole (0.80 g, 0.0022 mol) and triethylamine in CH_2Cl_2 (10 ml). The mixture was then stirred at room temperature for 19 h. The CH_2Cl_2-solution was washed with water, dried ($MgSO_4$) and the solvent was evaporated giving the desired product as an oil (0.06 g, 6%). NMR data for the final product is given below.

Example 7. Method d. Preparation of N[1] - (N′ - phenylcarbamoyl) - 5,6 - methylenedioxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) - methyl] sulfinyl] - 1*H* - benzimidazole.

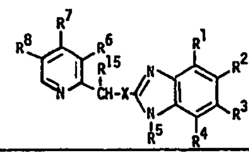
Phenylisocyanate (0.20 g, 0.00167 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring to a solution of 5,6 - methylenedioxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl) - methyl] sulfinyl] - 1*H* - benzimidazole (0.50 g, 0.00139 mol) and triethylamine (0.28 g, 0.00278 mol) in CH_2CL_2 (15 ml). The mixture was then stirred at room temperature for 50 hours. The CH_2Cl_2-solution was washed with water, dried ($MgSO_4$) and the solvent was evaporated giving the desired product as an oil (0.03 g, 5%). NMR data for the final products is given below.

Example 8. Method e. Preparation of 4,6-dimethyl - 5 - methoxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl)methyl]sulfinyl] - 1*H* - benzimidazole.

N[1] - Propionyl - 4,6 - dimethyl - 5 - methoxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl)methyl]sulfinyl] - 1*H* - benzimidazole (1.0 g, 0.0023 mol) was heated in 1M NaOH (15 ml) for 1 h under stirring and N_2-atmosphere, pH was adjusted to 9.5 by addition of 2M HCl. Extraction with CH_2Cl_2, separation of the phases, drying the organic phase, evaporation of the solvent and recrystallization from CH_3CN gave the desired product (0.30 g, 35%), m.p. 137°C.

The following Table 2 gives data for further examples of compounds of the invention.

Table 2. Summary of working examples.

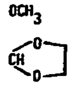
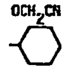
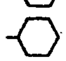


Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
9	S	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	82	164–165
10	SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 2)	73	146–148
11	S	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3	b (Ex 3)	79	207
12	SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3	a (Ex 2)	32	193
13	S	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	97	165
14	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 2)	59	147
15	S	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	79	159
16	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	83	188
17	S	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	77	NMR

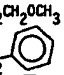
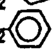
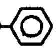
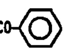
cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
18	SO	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	58	129
19	S	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3	b (Ex 3)	79	163
20	SO	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3	a (Ex 1)	52	191
21	S	H	CH_3	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	37	109
22	SO	H	CH_3	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	58	149
23	S	H	H	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	99	181
24	SO	H	H	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	71	157
25	S	H	CH_3	H	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	62	NMR
26	SO	H	CH_3	H	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	10	155
27	S	H	CH_3	H	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	90	NMR
28	SO	H	CH_3	H	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	69	142
29	S	H	H	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	74	NMR
30	SO	H	H	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	55	134
31	S	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	51	105-107
32	SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	62	111
33	S	H	H	OCH_3	H	H	H	CH_3	$OCH_2C{\equiv}CH$	CH_3	b (Ex 3)	66	154

cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
34	SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2C{\equiv}CH$	CH_3	a (Ex 1)	71	145
35	SO	H	H	OCH_3	H	H	H	H	OCH_3	C_2H_5	a (Ex 1)	31	147
36	S	H	H	OCH_3	H	H	H	H		$-(CH_2)_4-$	b (Ex 3)	61	NMR
37	SO	H	H	OCH_3	H	H	H	H		$-(CH_2)_4-$	a (Ex 2)	34	NMR
38	S	H	H		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	22	148
40	S	H	CH_3	H	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	76	134-136
41	SO	H	CH_3	H	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	35	111
42	S	H	H	OCH_2CN	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	29	66
43	SO	H	H	OCH_2CN	H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	39	94
44	S	H	H		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	75	NMR
45	SO	H	H		H	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	60	155

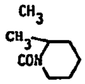
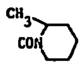
cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(^oC) other data
47	SO	H	H	$COOCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	a		
48	S	H	H	$COOCH_2$-	CH_3	H	H	CH_3	OCH_3	CH_3	c		
49	SO	H	H	$COOCH_2$-	CH_3	H	H	CH_3	OCH_3	CH_3	a		
50	S	H	H	CH_2OH	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	86	192
51	SO	H	H	CH_2OH	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	10	169
52	S	H	H	CH_2OCO-	CH_3	H	H	CH_3	OCH_3	CH_3	c		
53	SO	H	H	CH_2OCO-	CH_3	H	H	CH_3	OCH_3	CH_3	a		
54	S	H	H	$COOCH_3$	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	75	168
55	SO	H	H	$COOCH_3$	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 1)	52	139
56	S	H	CH_3	OCH_3	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	70	NMR
8	SO	H	CH_3	OCH_3	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 1) e (Ex 8)	56 35	137 137
3	S	H	CH_3	OCH_3	CH_3	H	H	CH_3	CH_3	H	b (Ex 3)	67	NMR
1	SO	H	CH_3	OCH_3	CH_3	H	H	CH_3	CH_3	H	a (Ex 1)	32	161
57	S	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	90	NMR
58	SO	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	68	144

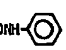
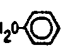
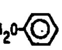
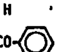
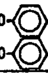
cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(^oC) other data
59	S	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	H	CH_3	CH_3	b (Ex 3)	95	NMR
60	SO	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	H	CH_3	CH_3	a (Ex 1)	58	131
61	S	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	90	192-4
62	SO	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	25	164-5
63	S	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	H	CH_3	b (Ex 3)	99	184-6
64	SO	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	H	CH_3	a (Ex 2)	91	148-50
65	S	H	CH_3	COC_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	68	149
66	SO	H	CH_3	COC_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	48	NMR
67	S	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	91	182
68	SO	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	67	175-7
69	S	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	H	b (Ex 3)	95	NMR
70	SO	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	H	a (Ex 2)	73	142-3
71	S	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	82	150
72	SO	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	81	180
73	S	H	CH_3	OCH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3	b (Ex 3)	82	143
74	SO	H	CH_3	OCH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3	a (Ex 2)	43	163

cont.

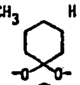
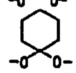
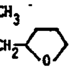
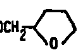
Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
75	S	H	Cl	Cl	Cl	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	90	204
76	SO	H	Cl	Cl	Cl	H	H	CH_3	OCH_3	CH_3	a		
77	SO	H	H	CH_3	CH_3	H	H	H	OCH_3	C_2H_5	a (Ex 1)	43	156
78	S	H	H		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	90	NMR
79	SO	H	H		H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	61	NMR
80	S	H	H	$-OCH_2O-$		H	H	CH_3	OCH_3	CH_3	b (Ex 3)	91	168
81	SO	H	H	$-OCH_2O-$		H	H	CH_3	OCH_3	CH_3	a (Ex 1)	67	165
82	S	H	-CH=CH-CH=CH-		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	73	NMR
83	SO	H	-CH=CH-CH=CH-		H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	60	184
84	S	H	H	-CH=CH-CH=CH-		H	H	CH_3	OCH_3	CH_3	b (Ex 3)	78	191
85	SO	H	H	-CH=CH-CH=CH-		H	H	CH_3	OCH_3	CH_3	a (Ex 1)	34	175
86	S	H	$-CH_2CH_2CH_2CH_2-$		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	58	NMR
87	SO	H	$-CH_2CH_2CH_2CH_2-$		H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	27	175
88	S	H	H	$-OCH_2O-$	.	H	CO_2CH_3	CH_3	OCH_3	CH_3	d		

cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
6	SO	H	H	$-OCH_2O-$		H	CO_2CH_3	CH_3	OCH_3	CH_3	d (Ex 6)	6	NMR
7	SO	H	H	$-OCH_2O-$		H	CONH- 	CH_3	OCH_3	CH_3	d (Ex 7)	5	NMR
90	S	H	H	$OCH_2CH_2CH_2O-$ 	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	25	NMR
91	SO	H	H	$OCH_2CH_2CH_2O-$ 	H	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	78	61
92	S	H	CH_3	$O(CH_2)_6CH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	64	NMR
2	SO	H	CH_3	$O(CH_2)_6CH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	32	116
93	S	H	H	C_2H_5	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3	b (Ex 3)	45	NMR
94	SO	H	H	C_2H_5	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3	a (Ex 1)	49	124-6
95	S	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3	b (Ex 3)	55	NMR
96	SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3	a (Ex 1)	33	111
97	S	H	$-CH=CH-CH=C-CH_2CH_2-$			H	H	CH_3	OCH_3	CH_3	b (Ex 3)	96	190
98	SO	H	$-CH=CH-CH=C-CH_2CH_2-$			H	H	CH_3	OCH_3	CH_3	a (Ex 2)	93	109
4	S	H	H	OCH_3	H	H	CO- 	CH_3	OCH_3	CH_3	d (Ex 4)	48	NMR
5	S	H	H	H	OCH_3	H	CO- 	CH_3	OCH_3	CH_3	d (Ex 5)		

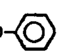
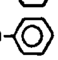
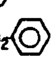
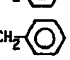
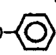
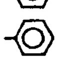
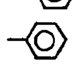
cont.

Table 2 cont.

Ex.	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
99	S	H	H	$CH(CH_3)_2$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	99	70
101	S	H	H	$C(CH_3)_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	52	88-89
102	SO	H	H	$C(CH_3)_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 2)	12	NMR
103	S	H	H	$CH_2CH_2OCH_3$	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	84	NMR
104	SO	H	H	$CH_2CH_2OCH_3$	H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	38	118
105	S	H	H			H	H	CH_3	OCH_3	CH_3	b (Ex 3)	58	216
106	SO	H	H			H	H	CH_3	OCH_3	CH_3	a (Ex 2)	32	158
107	SO	H	H	OCH_3	H	H	CO_2CH_3	CH_3	OCH_3	CH_3	d (Ex 4 and 5)	6	NMR
108	SO	H	H	H	OCH_3	H	CO_2CH_3	CH_3	OCH_3	CH_3	d (Ex 4 and 5)	6	NMR
109	S	H	H	SCH_3	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	83	147-148
110	S	H	H	$CH(CH_3)_2$	H	H	H	CH_3	OCH_2-	CH_3	b (Ex 3)	86	^1H NMR
111	SO	H	H	$CH(CH_3)_2$	H	H	H	CH_3	OCH_2-	CH_3	a (Ex 2)	89	^1H NMR

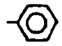
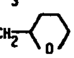
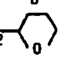
cont.

Table 2 cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p.(°C) other data
112	S	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	40	^1H NMR
113	SO	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 2)	28	123-4
114	S	H	H	C(=O)H	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	21	162
115	S	H	H	OCH_3	H	H	H	-CH=CH-CH=CH-		H	b (Ex 3)	67	105
116	SO	H	H	OCH_3	H	H	H	-CH=CH-CH=CH-		H	a (Ex 1)	66	100
117	S	H	H	O-	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	98	122
118	SO	H	H	O-	H	H	H	CH_3	OCH_3	CH_3	a (Ex2)	80	118
119	S	H	H	OCH_2CH_2-	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	80	^1H NMR
120	SO	H	H	OCH_2CH_2-	H	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	55	145 d
121	S	H	H	CO-	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	82	^1H NMR
122	SO	H	H	CO-	H	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	24	^1H NMR
123	S	H	H		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	88	158

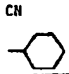
cont.

Table 2 cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method Ex. No.)	Yield %	M.p. (°C) other data
124	SO	H	H		H	H	H	CH_3	OCH_3	CH_3	a (Ex 2)	52	104
125	S	H	H	$SOCH_3$	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	57	^{1}H NMR
126	SO	H	H	$SOCH_3$	H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	47	^{1}H NMR
127	SO	H	H	NO_2	H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	14	^{1}H NMR
128	S	H	H	Br	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	b (Ex 3)	64	171
129	SO	H	H	Br	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	a (Ex 2)	58	143
130	S	H	H	OCH_3	H	H	H	-CH=CH-O-		H	b (Ex 3)	77	NMR
131	SO	H	H	OCH_3	H	H	H	-CH=CH-O-		H	a (Ex 2)	19	NMR
132	SO	H	H	CH_3	CH_3	H	$\overset{O}{C}OC(CH_3)_3$	CH_3	OCH_3	CH_3	d (Ex 6)	22	168
134	SO	H	H	CH_3	CH_3	H	$\overset{O}{C}N(CH_3)_2$	CH_3	OCH_3	CH_3	d (Ex 6)	21	^{1}H NMR
135	S	H	H	CH_3	CH_3	H	H	CH_3	OCH_2- 	CH_3			
136	SO	H	H	CH_3	CH_3	H	H	CH_3	OCH_2- 	CH_3			
137	S	H	H		$-CH_2CH_2CH_2-$	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	74	160
138	SO	H	H		$-CH_2CH_2CH_2-$	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	40	171

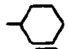
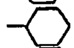
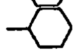
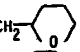
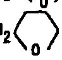
cont.

Table 2 cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method (Ex. No.)	Yield %	M.p. (°C) other data
139	S	H	-CH=CH-CH=N-		H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	38	NMR
140	SO	H	-CH=CH-CH=N-		H	H	H	CH_3	OCH_3	CH_3	a (Ex 1)	26	60
141	S	H	H		$-OCH_2O-$	H	H	CH_3	CH_3	CH_3	b (Ex 3)	83	193-95
142	SO	H	H		OCH_2O	H	H	CH_3	CH_3	CH_3	a (Ex 2)	76	173
143	SO	H	H	$\overset{O}{C}OCH_3$	CH_3	H	H	H	OCH_3	C_2H_5	a (Ex 2)	49	154
144	S	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	H	b (Ex 3)	39	^{1}H NMR
145	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	H	a (Ex 2)	65	^{1}H NMR
146	S	H	CH_3	CH_3	CH_3	H	H	H	CH_3	CH_3	b (Ex 3)	78	143
147	SO	H	CH_3	CH_3	CH_3	H	H	H	CH_3	CH_3	a (Ex 2)	64	180
148	S	H	CH_3	CH_3	CH_3	H	H	CH_3	H	CH_3	b (Ex 3)	70	239-42
149	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	H	CH_3	a (Ex 2)	14	171
150	S	H	CH_3	CH_3	H	CH_3	H	CH_3	CH_3	H	b (Ex 3)	96	210
151	SO	H	CH_3	CH_3	H	CH_3	H	CH_3	CH_3	H	a (Ex 2)	66	^{1}H NMR
152	S	H	CH_3	CN	CH_3	H	H	CH_3	OC_2H_5	CH_3	b (Ex 3)	94	151
153	SO	H	CH_3	CN	CH_3	H	H	CH_3	OC_2H_5	CH_3	1 (Ex 2)	29	150
154	S	H	H		H	H	H	H	CH_3	C_2H_5	b (Ex 3)	48	^{1}H NMR

cont.

Table 2 cont.

Ex	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Mehtod (Ex. No.)	Yield %	M.p. (°C) other data
155	SO	H	H		H	H	H	H	CH_3	C_2H_5	a (Ex 2)	44	105
156	S	H	H		H	H	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	b (Ex 3)	94	^1H NMR
157	SO	H	H		H	H	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	a (Ex 2)	18	181
158	S	H	H	CF_3	H	H	H	CH_3	OCH_2	CH_3	b (Ex 3)	67	100
159	SO	H	H	CF_3	H	H	H	CH_3	OCH_2	CH_3	a (Ex 2)	57	125
160	S	H	H	$CH_2CH_2COOC_2H_5$	H	H	H	CH_3	OCH_3	CH_3	b (Ex 3)	15	^1H NMR
161	SO	H	H	OCH_3	H	H	$\overset{O}{\overset{\parallel}{C}}-OC(CH_3)_3$	CH_3	OCH_3	CH_3	d (Ex 6)	50	155
163	SO	H	H	OCH_3	H	H	H	$-CH_2CH_2O-$		H			
164	S	H	H	OCH_3	H	H	H	$-CH_2CH_2CH_2O-$		H	b (Ex 3)	71	^1H NMR
165	SO	H	H	OCH_3	H	H	H	H	$-OCH_2CH_2-$				
166	SO	H	H	OCH_3	H	H	H	H	$-OCH_2CH_2CH_2-$				

Identifying data for compounds of the invention

NMR-data of the compounds in Table 2 (90 MHz)

Example No.	NMR-data: $\delta(CDCl_3)$ ppm
17	2.3(s,3H), 2.35(d,6H), 2.5(s,3H), 2.55(s,3H), 4.4(s,2H), 4.25-4.4(d,2H), 5.2-5.6(m,2H), 5.9-6.4(m,1H), 6.9(s,1H), 8.35(s,1H).
25	
27	2.2(s,3H), 2.3(s,3H), 2.6(s,3H), 4.35-4.45(d,2H), 4.45(s,2H), 5.2-5.6(m,2H), 5.85-6.35(m,1H), 6.9-7.55(m,3H), 8.3(s,1H).
29	2.2(s,3H), 2.25(s,3H), 2.4(s,3H), 4.2-4.35(d,2H), 4.4(s,2H), 5.5-5.6(m,2H), 5.85-6.3(m,1H), 6.9-7.1(d,1H), 7.3-7.55(t,2H), 8.3(s,1H).
36	1.8(m,4H), 2.75(m,4H), 3.8(s,3H), 4.25(s,2H), 6.85(m,1H), 7.05(s,2H), 7.4(d,1H), 8.3(s,1H).
37	1.7(m,4H), 2.3-2.7(m,4H), 3.85(s,3H), 4.6(d,2H), 6.8(s,1H), 7.05(s,2H), 7.6(m,1H), 8.3(s,1H).
44	1.2-2.0(m,10H), 2.25(s,3H), 2.3(s,3H), 2.6(m,1H), 3.75(s,3H), 4.45(s,2H), 7.1(q,1H), 7.5(m,2H), 8.35(s,1H).
56	

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: $\delta(CDCl_3)$ ppm
3	2.3(s,6H), 2.35(s,3H), 2.5(s,3H), 3.75(s,3H), 4.4(s,2H), 7.05-7.2(d,1H), 7.25(s,1H), 8.3-8.45(d,1H).
57	2.2(s,3H), 2.25(s,3H), 2.3(s,3H), 2.5(s,3H), 3.45(s,3H), 3.75(s,3H), 3.85(m,4H), 4.3(s,2H), 7.2(br.s., 1H), 8.3(s,1H).
59	2.3(s,6H), 2.4(s,3H), 2.55(s,3H), 3.5(s,3H), 3.9(m,4H), 4.3(s,2H), 7.2(s,1H), 7.3(s,1H), 8.4(s,1H), 9.3(br.s., 1H).
66	1.2(t,3H), 2.15(s,3H), 2.2(s,3H), 2.3(s,3H), 2.4(s,3H), 2.8(q,2H), 3.65(s,3H), 4.8(s,2H), 7.3(s,1H), 8.25(s,1H).
69	1.1(t,3H), 2.2(s,3H), 2.4(s,3H), 2.55(s,3H), 2.75(q,2H), 3.85(s,3H), 4.35(s,2H), 6.75(d,1H), 7.25(s,1H), 8.4(d,1H).
78	1.2(d,3H), 1.6(m,6H), 2.25(s,3H), 2.3(s,3H), 3.0(m,1H), 3.75(s,3H), 4.15(m,1H), 4.45(s,2H), 4.55(m,1H), 7.3(q,1H), 7.6(m,2H), 8.3(s,1H).
79	1.25(d,3H), 1.65(m,6H), 2.15(s,3H), 2.2(s,3H), 3.1(m,1H), 3.65(s,3H), 4.1(m,1H), 4.6(m,1H), 4.8(s,2H), 7.4(q,1H), 7.7(d,1H), 7.8(s,1H), 8.3(s,1H).
82	2.2(s,3H), 2.3(s,3H), 3.7(s,3H), 4.75(s,2H), 7.3-8.5(m,8H).

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ($CDCl_3$) ppm
86	1.85(m,4H), 2.2(s,3H), 2.25(s,3H), 2.7-3.1(m,4H), 3.75(s,3H), 4.35(s,2H), 6.9(d,1H), 7.3(d,1H), 8.25(s,1H).
6	2.2(s,3H), 2.35(s,3H), 3.8(s,3H), 4.15(s,3H), 4.75(s,2H), 6.1(s,2H), 7.3(s,1H), 7.5(s,1H), 8.15(s,1H).
7	2.15(s,3H), 2.2(s,3H), 3.7(s,3H), 4.7(s,2H), 6.05(s,2H), 7.0-7.6(m,7H), 8.15(s,1H), 8.3(s,1H).
90	2.25(s,3H), 2.1-2.4(m,2H), 2.3(s,3H), 3.75(s,3H), 4.2(t,4H), 4.4(s,2H), 6.75-7.2(m,5H), 7.2-7.6(m,3H), 8.35(s,1H).
92	0.7-2.05(m,13H), 2.25(s,3H), 2.3(s,3H), 2.35(s,3H), 2.5(s,3H), 3.65-3.9(m,2H), 3.75(s,3H), 4.35(s,2H), 7.2(s,1H), 8.3(s,1H).
93	1.25(t,3H), 2.25(s,3H), 2.3(s,3H), 2.8(q,2H), 4.4(d,2H), 4.45(s,2H), 5.2-5.65(m,2H), 5.85-6.3(m,1H), 7.0-7.65(m,2H), 7.5(s,1H), 8.35(s,1H).
95	0.9(s,3H), 1.0(s,3H), 1.5-1.95(m,2H), 2.15-2.45(m,1H), 2.25(s,3H), 2.3(s,3H), 3.7-4.0(t,2H), 3.85(s,3H), 4.45(s,2H), 2.8-7.0(m,1H), 7.15(d,1H), 7.45-7.55 (d,1H), 8.3(s,1H).
4+5	2.25(s,3H), 2.40(s,3H), 3.6 and 3.85(2s, total 3H), 3.80(s,3H), 4.8 and 4.85(2s,total 2H), 6.35-7.95 (m,8H), 8.35(s,1H).

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ($CDCl_3$) ppm
103	2.3(s,3H), 2.35(s,3H), 3.0(t,2H), 3.35(s,3H), 3.65(t,2H), 3.8(s,3H), 4.4(s,2H), 6.8-7.6(m,4H), 8.25(s,1H).
107+108	2.2(s,3H), 2.35(s,3H), 3.75(s,3H), 3.9 and 3.95 (2s,total 3H), 4.15(s,3H), 4.75(s,2H), 7.07-7.95 (m,3H), 8.15(s,1H).
102	1.32(s,9H), 2.08(s,3H), 2.15(s,3H), 4.09(d,2H), 4.74(s,2H), 5.10-5.45(m,2H), 5.73-6.25(m,1H), 7.28-7.73(m,3H), 8.27(s,1H).
139	2.22(s,3H), 2.29(s,3H), 3.75(s,3H), 4.40(s,2H), 7.38-7.58(m,1H), 7.87-8.02(m,2H), 8.29-8.47(m,1H), 8.70-9.00(m,2H).
110	1.25(d,6H), 1.6-2.15(m,4H), 2.25(s,3H), 2.3(s,3H), 3.0(m,1H), 3.7-4.05(m,4H), 4.25(m,1H), 4.5(s,2H), 7.15(q,1H), 7.5(s,1H), 7.55(d,1H), 8.3(s,1H).
111	1.3(d,6H), 1.55-2.15(m,4H), 2.2(s,3H), 2.25(s,3H), 3.05(m,1H), 3.65(d,2H), 3.9(m,2H), 4.2(m,1H), 4.8 (s,2H), 7.3(d,1H), 7.4-7.8(m,2H), 8.3(s,1H).
119	2.3(s,3H), 2.35(s,3H), 3.15(t,2H), 3.7(s,3H), 4.25(t,2H), 4.4(s,2H), 6.9(q,1H), 7.15(d,1H), 7.3-7.6(m,6H), 8.35(s,1H).
125	2.3(s,3H), 2.35(s,3H), 2.8(s,3H), 3.8(s,3H), 4.5 (s,2H), 7.5(d,1H), 7.75(d,1H), 8.05(s,1H), 8.4(s,1H).

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: $\delta(CDCl_3)$ ppm
126	2.2(s,6H), 2.8(s,3H), 3.7(s,3H), 4.85(s,2H), 7.6 (q,1H), 7.85(d,1H), 8.15(s,1H), 8.25(s,1H).
127	2.25(d,6H), 3.75(s,3H), 4.9(d,2H), 7.8(d,1H), 8.3(s,1H), 8.3(q,1H), 8.65(d,1H).
134	2.2(d,6H), 2.35(d,6H), 3.1(s,6H), 3.7(s,3H), 4.95 (s,2H), 7.2(s,1H), 7.6(s,1H), 8.3(s,1H).
112	2.1(s,3H), 2.25(s,3H), 2.3(s,3H), 2.65-3.2(m,4H), 4.4(d.2H), 4.42(s,2H), 5.2-5.6(m,2H), 5.9-6.4(m,1H), 7.1(dd,1H), 7.4(d,1H), 7.5(d,1H), 8.35(s,1H).
121	2.25(s,3H), 2.35(s,3H), 3.8(s,3H), 4.45(s,2H), 7.45-8.0(m,7H), 8.15(s,1H), 8.4(s,1H).
122	2.2(s,6H), 3.7(s,3H), 4.8(d,2H), 7.5-8.05(m,7H), 8.2(s,1H), 8.25(s,1H).
144	2.25(s,3H), 2.35(s,6H), 2.38(s,3H), 2.55(s,3H), 4.4(s,2H), 7.15(d,1H), 7.3(s,1H), 8.4(d,1H).
145	2.15(s,3H), 2.23(s,3H), 2.27(s,3H), 2.4(s,3H), 2.47(s,3H), 4.8(s,2H), 7.1(d,1H), 7.3(s,1H), 8.37(d,1H).
151	2.2(s,3H), 2.23(s,3H), 2.35(s,3H), 2.4(s,3H), 2.47(s,3H), 4.8(d,2H), 7.0(s,1H), 7.1(d,1H), 8.37 (d,1H).
130	3.85(s,3H), 4.65(s,2H), 6.8-7.8(m,7H), 8.55(d,1H)

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: $\delta(CDCl_3)$ ppm
131	3.85(s,3H), 4.95(d,2H), 6.65-7.60(m,7H), 8.45(d,1H).
160	1.15(t,3H), 2.20(s,3H), 2.27(s,3H), 2.49-2.73(m,2H), 2.89-3.13(m,2H), 3.72(s,3H), 4.09(q,2H), 4.37(s,2H), 6.98 and 7.08(dd,1H), 7.30-7.55(m,2H), 8.28(s,1H).
154	1.1-2.1(m,13H),2.3(s,3H),2.5-2.8(m,3H), 4.4(s,2H), 7.1-7.65(m,4H), 8.5(s,1H)
156	1.1-2.0(m,11H), 2.25(s,3H), 2.3(s,3H), 3.45(s,3H), 3.7(t,2H), 4.0(t,2H), 4.4(s,2H), 7.05-7.65(m,3H), 8.35(s,1H)
164 (270 MHz)	2.13(m,2H),2.88(t,2H),3.82(s,3H),4.26(t,2H), 4.69(s,2H),6.7-6.85(m,2H),7.04(d,1H), 7.39(d,1H),8.1(d,1H).

Preparation of intermediates

Example 11. Method A. Preparation of 4,5,7-trimethyl-2-mercapto-1*H*-benzimidazole.

2-Nitro-3,4,6-trimethylaniline (10.2 g, 0.057 mol) was diss lved in 95% ethan l (900 ml) and hydrogenated in the presence of Pd/C-catalyst until the theoretical amount of hydrogen had been consumed (1 hour). The whole mixture was transferred to another flask and potassium ethylxanthate (12.8 g, 0.080 mol) dissolved in water (12.5 ml) was added. The mixture was refluxed overnight, 2M NaOH (20 ml) was added and the volatiles were evaporated off. The residue was dissolved in methanol (300 ml) and the catalyst was filtered off. Part of the solvent (200 ml) was evaporated off. Water (100 ml) was added and the mixture was acidified with acetic acid (10 ml) dissolved in water (20 ml). The crystalline precipitate was filtered off, washed with water and dried under reduced pressure, giving the desired product (7.2 g, 66%), NMR: δ($COCl_3$) 2.0(s,3H), 2.05(s,3H), 2.1(s,3H), 3.3(br.s,1H), 6.5(s,1H).

Example 12. Method B. Preparation of 4,6,7-trimethyl-5-methoxy-2-mercapto-1*H*-benzimidazole.

A solution of 4-methoxy-3,5,6-trimethyl-1,2-phenylenediamine (1.8 g, 0.010 mol) and triethylamine (2.1 g), 0.021 mol) in $CHCl_3$ (15 ml) was added dropwise to a stirred solution of thiophosgene (0.60 g, 0.0052 mol) in $CHCl_3$ (5 ml). The mixture was then stirred at room temperature for 1 hour. Water (15 ml) and triethylamine (0.5 g) was added and the mixture was stirred for 1 hour. The precipitate was filtered off, washed with water and dried in the air giving the desired product (0.96 g, 43%), NMR: δ($COCl_3$) 2.5(s,3H), 2.65(s,6H), 3.65(s,3H), 12.0(br.s.,1H).

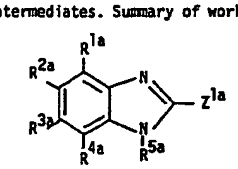
Example 13. M th d C. Preparation of 4-allyloxy-3,5-dimethyl-2-pyridinyl-methanol.

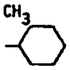
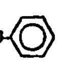
4-Allyloxy-2,3,5-trimethyl-pyridine N-oxide (4.0 g, 0.021 mol) was added dropwise under stirring to acetic anhydride (8.0 ml, 0.062 mol) preheated to 80°C, giving a final temperature of 120°C. The mixture was then heated at 80°C for 1 hour. Methanol (15.0 ml) was added and the mixture was kept at 80°C for 15 min. The volatiles were evaporated under reduced pressure. 10% HCl (20ml) was added and the mixture was heated at 90°C for 1 hour and then cooled to room temperature. Excess 2M NaOH was added and the mixture was extracted with CH_2Cl_2. The organic phase was separated out and dried. Volatiles were evaporated off giving the desired product as an oil (3.0 g, 75%), NMR: δ($COCl_3$) 2.1(s,3H), 2.25(s,3H), 4.4(m,2H), 4.65(s,2H), 4.75(s, 1H), 5.2-5.65(m,2H), 5.9-6.45(m,1H), 8.3(s,1H).

Example 14. Method D. Preparation of 4-allyloxy-3,5-dimethyl-2-pyridinyl-methyl chloride hydrochloride.

Thionyl chloride (4.0 ml) dissolved in CH_2Cl_2 (12 ml) was added dropwise to a stirred solution of 4-allyloxy-3,5-dimethyl-2-pyridinylmethanol (8.0 g, 0.041 mol) in CH_2Cl_2 (50 ml), maintaining the temperature below 6°C. Then the mixture was stirred at room temperature for 45 min (final temperature 15°C). Isopropanol (2 ml) was added and the solution was heated shortly at 35°C. The solvent was evaporated off and the crystalline residue was recrystallized from ethanol/ether giving the desired product (3.0 g, 29%), m.p. 115°C.

Table 3a. Intermediates. Summary of working examples.

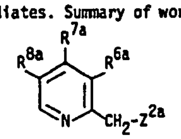


No.	Z^{1a}	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	Method[x)] (Ex. No.)	Yield (%)	Mp (°C) other data
I5	SH	CH_3	CH_3	CH_3	CH_3	H	A(Ex I1)	19	NMR
I6	SH	CH_3	CH_3	CH_3	H	H	A(Ex I1)	66	NMR
I1	SH	CH_3	CH_3	H	CH_3	H	A(Ex I1)	66	NMR
I7	SH	H		H	H	H	A(Ex I1)	71	NMR
I8	SH	CH_3	OCH_3	CH_3	H	H	A(Ex I1)	78	NMR
I9	SH	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	A(Ex I1)	85	NMR
I10	SH	CH_3	C_2H_5	CH_3	H	H	A(Ex I1)	89	NMR
I11	SH	H	8} $OCH_2CH_2CH_2O$- 	H	H	H	A(Ex I1)	14	167
I12	SH	CH_3	$O(CH_2)_6CH_3$	CH_3	H	H	A(Ex I1)	73	NMR
I2	SH	CH_3	OCH_3	CH_3	CH_3	H	B(Ex I2)	43	NMR
I13	SH	-CH=CH-CH=CH-CH_2CH_2-			H	H	A(Ex I1)	23	NMR

x) Method A: The 1,2-phenylenediamine is reacted with $C_2H_5OCS_2K$

Method B: The 1,2-phenylenediamine is reacted with $CSCl_2$

Table 3b. Intermediates. Summary of working examples.



No.	Z^{2a}	R^{6a}	R^{7a}	R^{8a}	Salt/Base	Method [xx] (Ex. No.)	Yield (%)	Mp (°C) other data
I3	OH	CH_3	$OCH_2CH{=}CH_2$	CH_3	Base	C(Ex I3)	75	NMR
I4	Cl	CH_3	$OCH_2CH{=}CH_2$	CH_3	HCl	D(Ex I4)	29	115°
I14	OH	CH_3	$OCH_2C{\equiv}CH$	CH_3	Base	C(Ex I3)	88	70°
I15	Cl	CH_3	$OCH_2C{\equiv}CH$	CH_3	HCl	D(Ex I4)	76	135°
I16	OH	H	$-(CH_2)_4-$		Base	C(Ex I3)	35	NMR
I17	Cl	H	$-(CH_2)_4-$		HCl	D(Ex I4)	72	NMR
I18	OH	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3	Base	C(Ex I3)	51	NMR
I19	Cl	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3	HCl	D(Ex I4)	95	
I20	OH	CH_3	OCH_2	CH_3	Base	C(Ex I3)	30	NMR
I21	Cl	CH_3	OCH_2	CH_3	HCl	D(Ex I4)	82	133
I22	OH	CH_3	OC_2H_5	CH_3	Base	C(Ex I3)	70	B.p. 120-26°C/0.4 mm
I23	Cl	CH_3	OC_2H_5	CH_3	HCl	D(Ex I4)	89	157
I24	OH	-CH=CH-O-		H	Base	C(Ex I3)	18	^1H NMR
I25	Cl	-CH=CH-O-		H	HCl	D(Ex I4)	95	195

[xx] Method C: Rearrangement of the pyridine N-oxide with $(CH_3CO)_2O$.
Method D: Chlorination with $SOCl_2$.

NMR—data of the compounds in Table 3a and Table 3b

Example No.	*NMR-data: δ(ppm)*
15	δ(DMSO-d_6) 2.05(s,6H), 2.2(s,6H).
16	δ($CDCl_3$) 2.05(s,3H), 2.15(s,3H), 2.2(s,3H), 3.2(s,2H), 6.7(s,1H).
11	δ($CDCl_3$) 2.0(s,3H), 2.05(s,3H), 2.1(s,3H), 3.3(br.s.,1H), 6.5(s,1H).
17	δ(DMSO-d_6) 1.1-2.05(m,10H), 2.4(m,1H), 6.85-7.05(m,3H).
18	δ(DMSO-d_6) 1.95(s,3H), 2.0(s,3H), 3.35(s,3H), 6.55(s,1H).
19	δ($CDCl_3$) 2.1(s,3H), 2.15(s,3H), 3.2(s,3H), 3.35-3.8(m,4H), 6.6(s,1H).
110	δ($CDCl_3$+DMSO-d_6) 1.05(t,3H), 2.3(s,3H), 2.35(s,3H), 2.6(q,2H), 6.85(s,1H).
112	δ($CDCl_3$) 0.5-1.7(m,13H), 2.0(s,3H), 2.1(s,3H), 3.15(s,2H), 3.35-3.6(m,2H), 6.6(s,1H).
12	δ($CDCl_3$) 2.5(s,3H), 2.65(s,6H), 3.65(s,3H), 12.0(br.s.,1H).
113	δ($CDCl_3$) 3.35(s,2H), 3.4(s,2H), 7.15-8.05(m,4H), 12.65(br.s.,1H), 13.3(br.s.,1H).
13	δ($CDCl_3$) 2.1(s,3H), 2.25(s,3H), 4.4(m,2H), 4.65(s,2H), 4.75(s,1H), 5.2-5.65(m,2H), 5.9-6.45(m,1H), 8.3(s,1H).
116	δ($CDCl_3$) 1.5-1.9(m,4H), 2.5-2.8(m,4H), 4.7(s,2H), 7.3(s,1H), 8.2(s,1H).
117	
118	δ($CDCl_3$) 1.0(s,3H), 1.05(s,3H), 1.5-2.05(m,3H), 2.15(s,3H), 2.3(s,3H), 3.75-4.0(t,2H), 4.15-4.5(br.s.,1H), 4.65(s,2H), 8.3(s,1H).
120	δ($CDCl_3$) 1.7-2.2(m,4H), 2.15(s,3H), 2.25(s,3H), 3.75- 4.05(m,4H), 4.15-4.4(m,1H), 4.6(s,2H), 8.25(s,1H).
124	δ($CDCl_3$) 8.55(d,1H), 7.8(d,1H), 7.5(d,1H), 7.0(d,1H), 5.1(s,2H).

Pharmaceutical preparations containing a compound of the invention as active ingredient are illustrated in the following examples.

Example 167. Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

4,6-Dimethyl-5-ethyl-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole-HCl	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavouring agent	0.05g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine w re dissolved in 60 g of warm water. After c oling the acid addition salt was dissolved in th sugar solution and glyc rol and a s luti n of flavouring agents dissolved in than l w r added. The mixtur was diluted with wat r t a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 168. Enteric-coated tablets

An enteric-coat d tablet containing 20 mg of active comp und was prepar d from th following ingredients:

I	5,6-Methyl nedioxy-2-[[(4-m thoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole	200 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I 5,6 - Methylenedioxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl)methyl]sulfinyl] - 1*H* - benzimidazole, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tabled cores (10 000 tablets), each tablet containing 20 mg of active substance, in a tabletting machine using 6 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota, Manesty (RTM) coating equipment. A final tablet weight of 110 mg was obtained.

Example 169. Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

4,6-Dimethyl-5-ethyl-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1*H*-benzimidazole	4 g
Polyethylene glycol 400 for injection	400 g
Disodium hydrogen phosphate	q.s.
Sterile water to a final volume of	1000 ml

4,6 - Dimethyl - 5 - ethyl - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl)methyl]thio] - 1*H*- benzimidazole was dissolved in polyethylene glycol 400 and 550 ml of water was added. pH of the solution was brought to pH 7.4 by adding a water solution of disodium hydrogen phosphate and water was added to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Biological tests

I. Inhibiting effect *in vitro* on acid secretion in isolated rabbit gastric glands

Test Method

Gastric gland preparation

Isolat d rabbit gastric glands were pr pared as described by B rglindh et al., Acta physiol. scand. 1976. 96. 150-159. This method inv lves vascular perfusion of the rabbit stomach via the gastric arteries, scraping and scissor mincing f the s parated gastric mucosa and collagenase (0.1%, Type I, Sigma Chemicals, St. Louis, MO. USA) digestion at 37°C for 60-90 min. The glands are then harvested and filtered through nylon cloth to remov coarse fragments. The glands are thereafter incubated at 37°C in a medium containing NaCl 132.4 mM, KCl 5.4 mM, NaH_2PO_4, 5.0 mM, NaH_2PO_4, 1.0 mM, $MgSO_4$ 1.2 mM, $CaCl_2$ 1.0 mM, glucose 10 mM, and 1 mg/ml rabbit albumine, pH 7.4.

Measurement of acid secretion

The acid secretion in the isolated gland preparation was recorded by measuring the uptake of ^{14}C-labelled aminopyrine into the glands as described by Berglindh et al., Acta physiol. scand. 1976. 97. 401-414. Accumulation of aminopyrine in the glands indicates gastric acid secretion within the glands. The standard medium contained 10^{-6}M ^{14}C-aminopyrine (Amersham, Great Britain). After the incubation period, the glands were centrifuged, the supernatant was removed and the glands dried, weighed and dissolved in Soluene-350 (Packard, IU. USA). Samples of the supernatant and glands were separately counted in a scintillation counter. The accumulation of ^{14}C-labelled aminopyrine in the glands was calculated as detailed by Berglindh et al., Acta physiol. scand. 1976. 97. 403.

Experimental protocol

Glands were incubated for 60 min. in the presence of 5×10^{-5}M histamine and the test compound to be studied. The free base of the test compound was dissolved in methanol. The final concentration of methanol was 1% in the incubation medium, having no influence on the aminopyrine accumulation ratio. For each test compound a complete dose-response curve was generated by testing doses in duplicate in the concentration range 10^{-7}M to 10^{-4}M. The logarithm of the concentration (in M) of the test compounds giving 50% inhibition of the aminopyrine accumulation in the glands (IC_{50}) is listed in Table 4 below.

II. Inhibiting effect *in vivo* on gastric acid secretion in conscious dog

Test Method

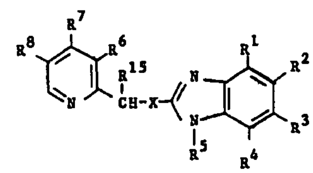
Chronic gastric fistula dogs were used. These dogs have been surgically provided with a gastric cannula in the stomach and a duodenal fistula used for direct introduodenal administration of test compounds. Following a 4 weeks' recovery period after surgery, tests were performed once a week on each dog. Food and water were withdrawn 18 hours before each test.

Gastric acid secretion was induced by continuous infusion of histamine at individual doses (100-300 nmol/kg, h), resulting in submaximal secretion of gastric acid. At least 2 hours after onset of stimulation, when the gastric acid secretion had reached a steady level, the test compounds in the form of free base suspended in 0.5% Methocel (RTM) (90 HG, 15.000, Dow Chem. Corp.), were given intraduodenally at doses from 1 to 8 µmol/kg. The gastric juice was collected by free flow from the gastric cannula in consecutive 30 minutes samples for 3 hours. The samples were titrated to pH 7.0 with 0.1 M NaOH using a Radiometer automatic titrator and th acid output was calculated.

The per cent inhibition of acid secretion was

calculated by comparing in each dog th acid output in the tests to the acid output in control tests when only the vehicle was given. The peak inhibitory effect for each compound is given in Table 5 bel w.

Table 4 Biological effects in isolated rabbit gastric glands



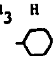
No.	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	$-\log IC_{50}$
12	SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3	6.5
16	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3	6.5
37	SO	H	H	OCH_3	H	H	H	H	$-(CH_2)_4-$		5.0
43	SO	H	H	OCH_2CN	H	H	H	CH_3	OCH_3	CH_3	4.4
51	SO	H	H	CH_2OH	CH_3	H	H	CH_3	OCH_3	CH_3	6.1
104	SO	H	H	$CH_2CH_2OCH_3$	H	H	H	CH_3	OCH_3	CH_3	5.7
8	SO	H	CH_3	OCH_3	CH_3	H	H	CH_3	OCH_3	CH_3	6.5
1	SO	H	CH_3	OCH_3	CH_3	H	H	CH_3	CH_3	H	6.7
58	SO	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	5.9
60	SO	H	CH_3	$OCH_2CH_2OCH_3$	CH_3	H	H	H	CH_3	CH_3	5.4
62	SO	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	6.2
64	SO	H	CH_3	$COCH_3$	CH_3	H	H	CH_3	H	CH_3	5.8
66	SO	H	CH_3	COC_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3	6.0
68	SO	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	CH_3	6.5
70	SO	H	CH_3	C_2H_5	CH_3	H	H	CH_3	OCH_3	H	5.9
72	SO	H	C_2H_5	CN	C_2H_5	H	H	CH_3	OCH_3	CH_3	5.0
74	SO	H	CH_3	OCH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3	6.2
79	SO	H	H	CH_3 CON	H	H	H	CH_3	OCH_3	CH_3	5.0
81	SO	H	H	$-OCH_2O-$		H	H	CH_3	OCH_3	CH_3	6.1
83	SO	H	$-CH{=}CH-CH{=}CH-$		H	H	H	CH_3	OCH_3	CH_3	5.5 / 5.3
107	SO	H	H	OCH_3	H	H	CO_2CH_3	CH_3	OCH_3	CH_3	5.8 (107 and 108)
108	SO	H	H	H	OCH_3	H	CO_2CH_3	CH_3	OCH_3	CH_3	

Cont.

cont.

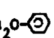
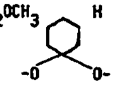
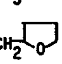
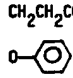
cont.

cont.

No.	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	$-\log IC_{50}$
10	SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	6.1
14	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	6.1
18	SO	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.9
20	SO	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3	6.0
22	SO	H	CH_3	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	6.0
24	SO	H	H	CH_3	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	6.0
26	SO	H	CH_3	H	H	CH_3	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.9
28	SO	H	CH_3	H	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.9
30	SO	H	H	CH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.9
32	SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.6
34	SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2C{\equiv}CH$	CH_3	5.0
35	SO	H	H	OCH_3	H	H	H	H	OCH_3	C_2H_5	5.6
41	SO	H	CH_3	H	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.9
45	SO	H	H		H	H	H	CH_3	OCH_3	CH_3	6.1

cont.

cont.

No.	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	$-\log IC_{50}$
55	SO	H	H	$COOCH_3$	CH_3	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.3
87	SO	H	$-CH_2CH_2CH_2CH_2-$		H	H	H	CH_3	OCH_3	CH_3	6.3
91	SO	H	H	$OCH_2CH_2CH_2O-$	H	H	H	CH_3	OCH_3	CH_3	5.8
2	SO	H	CH_3	$O(CH_2)_6CH_3$	CH_3	H	H	CH_3	OCH_3	CH_3	5.9
94	SO	H	H	C_2H_5	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	6.6
96	SO	H	H	OCH_3	H	H	H	CH_3	$OCH_2CH_2CH(CH_3)_2$	CH_3	6.1
98	SO	H	$-CH{=}CH-CH{=}CCH_2CH_2-$			H	H	CH_3	OCH_3	CH_3	5.6
102	SO	H	H	$C(CH_3)_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.9
104	SO	H	H	$CH_2CH_2OCH_3$	H	H	H	CH_3	OCH_3	CH_3	5.7
106	SO	H	H			H	H	CH_3	OCH_3	CH_3	6.0
111	SO	H	H	$CH(CH_3)_2$	H	H	H	CH_3	OCH_2	CH_3	6.2
113	SO	H	H	$CH_2CH_2COCH_3$	H	H	H	CH_3	$OCH_2CH{=}CH_2$	CH_3	5.8
118	SO	H	H		H	H	H	CH_3	OCH_3	CH_3	6.4

cont.

cont.

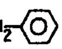
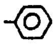
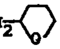
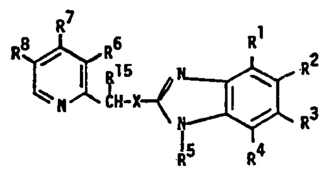
No.	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	-log IC_{50}
120	SO	H	H	OCH_2CH_2- 	H	H	H	CH_3	OCH_3	CH_3	6.3
124	SO	H	H		H	H	H	CH_3	OCH_3	CH_3	7.0
129	SO	H	H	Br	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3	
142	SO	H	H		$-OCH_2O-$	H	H	CH_3	CH_3	CH_3	6.0
143	SO	H	H	$\overset{O}{C}OCH_3$	CH_3	H	H	H	OCH_3	C_2H_5	6.1
145	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	CH_3	H	6.2
147	SO	H	CH_3	CH_3	CH_3	H	H	H	CH_3	CH_3	6.4
149	SO	H	CH_3	CH_3	CH_3	H	H	CH_3	H	CH_3	6.2
151	SO	H	CH_3	CH_3	H	CH_3	H	CH_3	CH_3	H	6.3
153	SO	H	CH_3	CN	CH_3	H	H	CH_3	OC_2H_5	CH_3	5.2
77	SO	H	H	CH_3	CH_3	H	H	H	OCH_3	C_2H_5	6.0
159	SO	H	H	CF_3	H	H	H	CH_3	OCH_2- 	CH_3	6.3

Table 5 Biological effects in conscious dogs



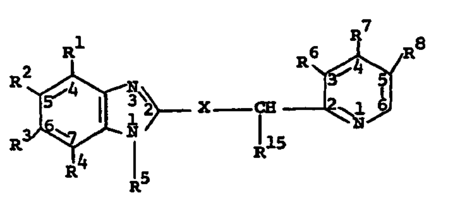
No.	X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	(I.D.) DOSE (µmol/kg)	% INHIB
84	S	H	H		-CH=CH-CH=CH-	H	H	CH_3	OCH_3	CH_3	8	85
109	S	H	H	SCH_3	H	H	H	CH_3	OCH_3	CH_3	8	60

Comment to the test results

It is seen in Table 4 and Table 5 that the tested compounds potently inhibited gastric acid secretion both in vitro and in vivo.

CLAIMS

1. A compound of the formula



I

wherein

X is —S— or $—\overset{O}{\overset{\uparrow}{S}}—$;

R^{15} is H, CH_3 or C_2H_5;

R^1, R^2, R^3 and R^4, which are th same or different, are

(a) H
(b) halogen
(c) —CN
(d) —CHO
(e) $—CF_3$
(f) $—\overset{O}{\overset{\|}{C}}—R^{11}$
(g) $—O—\overset{O}{\overset{\|}{C}}—R^{12}$
(h) $—CH(OR^{13})_2$
(i) $—(Z)_n—A—D$
(j) aryl
(k) aryloxy
(l) alkylthio containing 1-6 carbon atoms
(m) $—NO_2$
(n) alkylsulfinyl containing 1-6 carbon atoms or

wherein

(o) adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected fr m —N— and —O—, and which rings may b optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carb n at ms, alkylene radicals c ntaining 4-5 carbon atoms giving spiro comp unds, or two or four of these substituents together form one or two oxo groups.

$(\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—})$, whereby if R^1, R^2, R^3 and R^4 together with th adjacent carbon atoms in the benzimidazole ring form two rings they may b condens d with each other, in which formulas R^{11} and R^{12}, which are the same or different, are

(a) aryl,
(b) alkoxy containing 1-4 carbon atoms,
(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part,
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part,
(e) aryloxy,
(f) dialkylamino containing 1-3 carbon atoms in each alkyl residue, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is (a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is —O— or $\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—}$;

n is 0 or 1;

A is (a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms
(c) alkenylene containing 2-6 carbon atoms
(d) cycloalkenylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is (a) —CN
(b) $\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—}R^9$
(c) $\text{—}(Y)_m\text{—}(\overset{\text{O}}{\overset{\|}{\text{C}}})_r\text{—}R^{10}$

wherein

R^9 is (a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in each alkyl residue;

m is 0 or 1;

r is 0 or 1;

Y is (a) —O—
(b) —NH—
(c) $\text{—NR}^{10}\text{—}$;

R^{10} is (a) H
(b) alkyl containing 1-3 carbon atoms,
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part, or
(d) aryl;

R^5 is (a) H or
(b) $\text{-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-}R^{14}$;

wherein

R^{14} is (a) alkyl containing 1-6 carbon atoms,
(b) arylalkyl c ntaining 1-2 carbon atoms in the alkyl part
( ) aryl
(d) alk xy containing 1-4 carbon atoms
( ) arylalkoxy containing 1-2 carbon atoms in the alkyl part
(f) aryloxy
(g) amino
(h) mono- or dialkylamino containing 1-4 carbon atoms in each alkyl residu
(i) arylalkylamino containing 1-2 carbon atoms in th alkyl part
(j) arylamino;

R^6 and R^8, which are the same or different, are
(a) H or
(b) alkyl containing 1-5 carbon atoms;

R^7 is (a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms
(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) dialkylaminoalkoxy containing 1-2 carbon atoms in each of the alkyl residues on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(h) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(i) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(j) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
(k) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
(l) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring from a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

-CH=CH-CH=CH-
$\text{-O-(CH}_2\text{)}_p\text{-}$
$\text{-CH}_2\text{(CH}_2\text{)}_p\text{-}$
-O-CH=CH-
-NH-CH=CH-
$\text{-}\underset{\text{CH}_3}{\underset{|}{\text{N}}}\text{-CH=CH-}$

wherein p is 2, 3 or 4 and the O and N atoms always are attached to position 4 in the pyridine ring; and physiologically acceptable salts of the compounds I wherein X is S;

with the provisos that

(a) not more than one of R^6, R^7 and R^8 is hydrogen,
(b) when X is SO, R^5 is H and R^6, R^7 and R^8 are selected only from hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then those radicals R^1, R^2, R^3 and R^4 which are not H cannot be selected only from alkyl groups, halogen, alkoxycarbonyl, alkoxy or alkanoyl.
(c) when X is S, R^5 is H, alkanoyl or alkoxycarbonyl, and R^6, R^7 and R^8 are selected only from hydrogen, methyl, ethyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then those radicals R^1, R^2, R^3 and R^4 which are not H cannot be selected only from alkyl groups, hal g n, alkoxycarbonyl, alkoxy, alkanoyl, trifluoromethyl, or NO_2,
(d) when X is SO, one of R^6, R^7 and R^8 is H and the oth r two of R^6, R^7 and R^8 are alkyl, and at th same tim more than on of R^1, R^2, R^3 and R^4 ar hydrogen, then those radicals R^1, R^2, R^3 and R^4 which are not H cannot be selected only from alkyl, halogen, cyano,

$-\overset{O}{\overset{\|}{C}}$-(alk xy), (alkyl)-$O\overset{O}{\overset{\|}{C}}$-(alkyl)-, alkoxy, hydroxyalkyl, CF_3 or (alkyl)-$\overset{O}{\overset{\|}{C}}$-

(e) when R^3, R^4, R^5 and R^{15} are H and simultaneously R^6 and R^8 are H or CH_3 and R^7 is OCH_3, then R^1 is not CF_3 when R^2 is H, and R^2 is not CF_3 when R^1 is H.

2. A compound according to claim 1 wherein X=S.

3. A compound according to claim 1 wherein X=SO.

4. A compound according to any one of the preceding claims wherein R^5=H.

5. A compound according to any one of the preceding claims wherein R^{15}=H.

6. A compound according to any one of the preceding claims wherein at least three of the radicals R^1, R^2, R^3 and R^4 are other than hydrogen, or they form at least one ring.

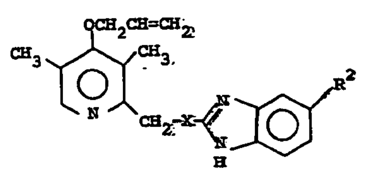
7. A compound according to any one of the preceding claims wherein R^1, R^2, R^3 and R^4 are selected from H, alkyl and alkoxy groups.

8. A compound according to any one of the preceding claims wherein R^6 and R^8 are selected from H, CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$ and ring structures connecting with position 4 in the pyridine ring.

9. A compound according to any one of the preceding claims wherein two of the radicals R^6, R^7 and R^8 form one ring structure and the third radical of R^6, R^7 and R^8 is H or alkyl.

10. A compound according to any one of claims 1-8 wherein R^5 and R^{15} are H; at least three of the radicals R^1, R^2, R^3 and R^4 are other than H; R^6 and R^8 are each H or CH_3; and R^7 is CH_3, OCH_3 or $OCH_2CH=CH_2$.

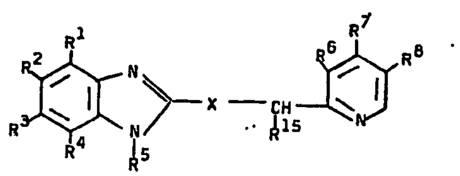
11. A compound of the formula:



wherein X is S or SO

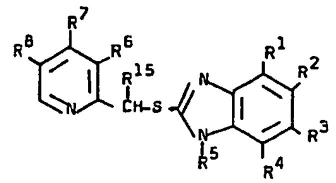
R^2 is CH_3, C_2H_5, $CH(CH_3)_2$ or OCH_3.

12. A process for the preparation of a compound of the formula:



I

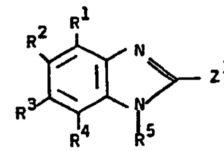
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^{15} are as defined in claim 1, and X is SO by oxidizing a comp und of the formula I,



I

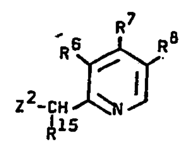
wherein R^{15}, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 have the meanings given above, to give a compound of the same formula I wherein X is SO;

13. Process for preparation of a compound of the formula I wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^{15} are as defined in claim 1 and X is S by reacting a compound of the formula:



II

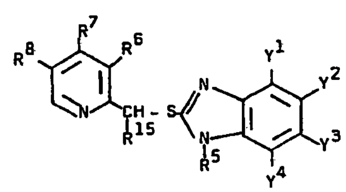
with a compound of the formula:



III

in which formulae R^{15}, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in claim 1 and wherein one of Z^1 and Z^2 is SH and the other is a leaving group, to give a compound of the formula I wherein X is S.

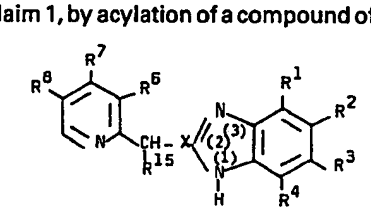
14. Process for the preparation of a compound of the formula I wherein X is S and at least one of R^1, R^2, R^3 and R^4 is an ester group $(Z)_n$-A-$COOR^9$, $COOR^{10}$ or $(Z)_n$-A-$OCOR^{10}$ wherein Z, n, A, R^9 and R^{10} are as defined in claim 1 by esterification of a compound of the formula:



IV

wherein R^{15}, R^5, R^6, R^7 and R^8 are as defined in claim 1 and Y^1, Y^2, Y^3 and Y^4 represent either R^1, R^2, R^3 and R^4 as defined in claim 1, respectively, or the groups $(Z)_n$-A-COOH, COOH and $(Z)_n$-A-OH, but at least one of Y^1, Y^2, Y^3, Y^4 is in the acid or alcohol form, by reaction with the appropriate alcohol R^9OH, $R^{10}OH$ or carboxylic acid $R^{10}COOH$, respectively, to form the required compound.

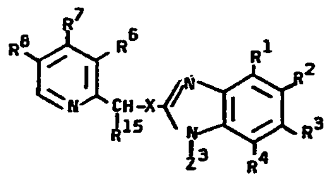
15. Process for preparation of a compound of the formula I wherein R^5 is $R^{14}CO$ and R^{14} is as d fined in claim 1, by acylation of a compound of the formula:



V

wherein R^{15}, X, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 are as defined in claim 1, by reaction with an appropriate acylating agent $(R^{14}CO)^2O$, or $R^{14}COX^1$, wherein X^1 is a l aving group.

16. Process for the preparation of a compound of the formula I wherein R^5 is H, by hydrolyzing a compound of the formula



VI

wherein X, R^{15}, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 are as defined in claim 1 and Z^3 is a suitable N-protecting group to form the required compound.

17. A process according to any one of claims 13-16 wherein a compound in which X is S is obtained and the resulting compound is converted into a physiologically acceptable salt.

18. A process according to any one of claims 12-17 substantially as hereinbefore described with reference to any one of the Examples.

19. A pharmaceutical composition containing a compound or salt according to any of claims 1-11 together with an inert carrier or diluent.

20. A composition according to claim 19 substantially as hereinbefore described with reference to any one of Examples 167-169.

21. A compound according to any one of claims 1-11 or a physiologically acceptable salt thereof or a composition according to claim 19 or 20 for use in a method of treatment of the human or animal body by surgery or therapy.

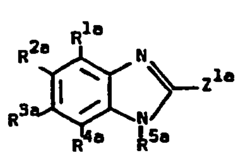
22. A compound according to any one of claims 1-11 or a physiologically acceptable salt thereof or a composition according to claim 19 or 20 for use in the treatment of gastric disorders.

23. A compound as defined in any of claims 1-11, or a therapeutically acceptable salt thereof, or a composition according to claim 19 or 20 for use in inhibiting gastric acid secretion in the human or animal body.

24. A compound as defined in any of claims 1-11, or a therapeutically acceptable salt thereof, or a composition according to claim 19 or 20 for use as a gastrointestinal cytoprotecting agent in the human or animal body.

25. A compound as defined in any of claims 1-11, or a therapeutically acceptable salt thereof, or a composition according to claim 19 or 20 for use in the treatment of gastrointestinal inflammatory diseases in the human or animal body.

26. A compound of the formula:



VIII

wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and selected from the groups

(a) H,

(b) alkyl containing 1-6 carbon atoms including cycloalkyl

( ) alkoxyalkyl containing 1-3 carbon atoms in th alkoxy residue and 1-6 carbon atoms in the alkyl residue,

(d) aryloxyalkyl containing 1-6 carbon atoms in the alkyl residue,

(e) arylalkyl containing 1-6 carbon atoms in the alkyl residue,

(f) aryl,

(g) alkoxy containing 1-6 carbon atoms,

(h) alkoxyalkoxy containing 1-3 carbon atoms in the outer alkoxy residue and 1-6 carbon atoms in the alkoxy residue nearest the aromatic ring,

(i) aryloxyalkoxy containing 1-6 carbon atoms in the alkoxy residue,

(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy residue, and

(k) aryloxy,

R^{5a} is (a) H,

(b) alkoxycarbonyl containing 1-4 carbon atoms in the alkoxy residue,

(c) arylalkoxycarbonyl containing 1-2 carbon atoms in the alkoxy residue,

(d) dialkylaminocarbonyl containing 1-4 carbon atoms in each alkyl residue, or

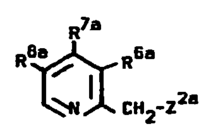
(e) arylaminocarbonyl,

and Z^{1a} is (a) SH,

(b) Cl or Br

provided that not more than one of R^{1a}, R^{2a}, R^{3a} and R^{4a} is H.

27. A compound of the formula:



IX

wherein R^{6a} and R^{8a} are

(a) H or

(b) alkyl containing 1-5 carbon atoms, and

R^{7a} is (a) alkenyloxy containing 2-5 carbon atoms, or

(b) alkynyloxy containing 2-5 carbon atoms,

(c) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms,

(d) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms,

(e) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(f) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

(g) R^{6a} and R^{7a}, or R^{7a} and R^{8a} together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a} is

—CH=CH—CH=CH—

$—O—(CH_2)_{pa}—$

$—CH_2—(CH_2)_{pa}—$

—O—CH=CH—

wherein pa is 2, 3 or 4 and the O atom always is attached to positi n R^{7a},

and Z^{2a} is (a) SH,

(b) halogen Cl, Br, I or

(c) OH

provided that not more than on f R^{6a} and R^{8a} is H.

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